ANNALS OF

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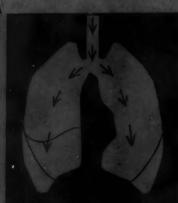
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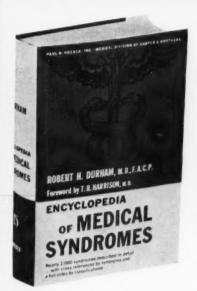
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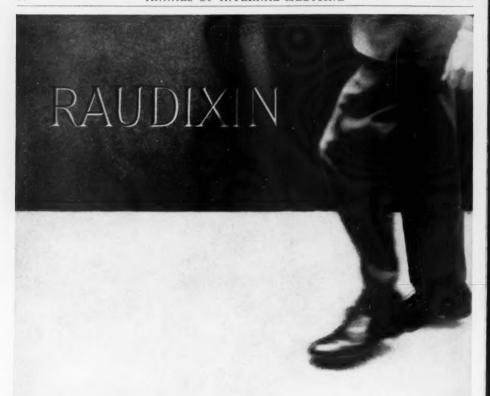
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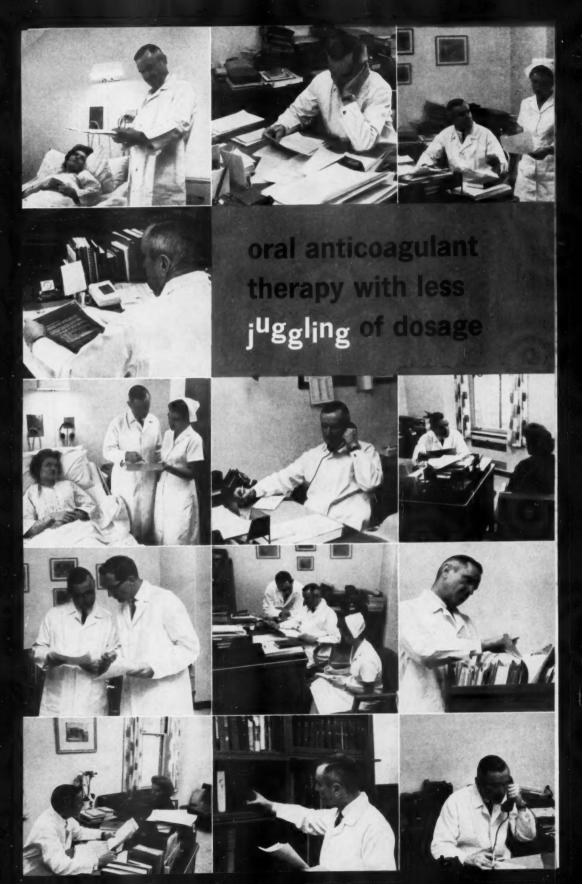
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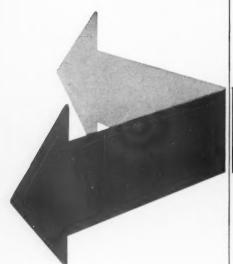
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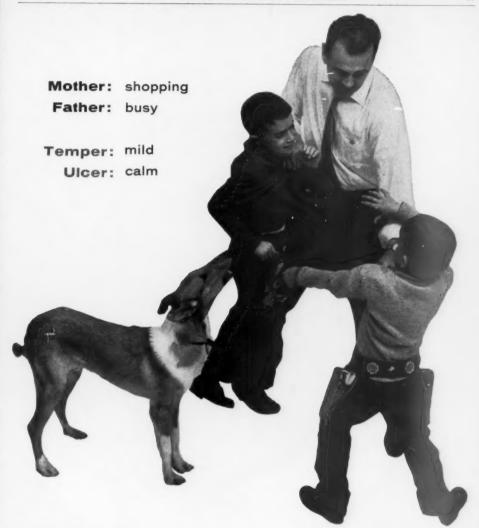
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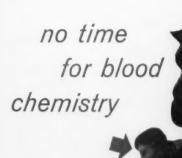
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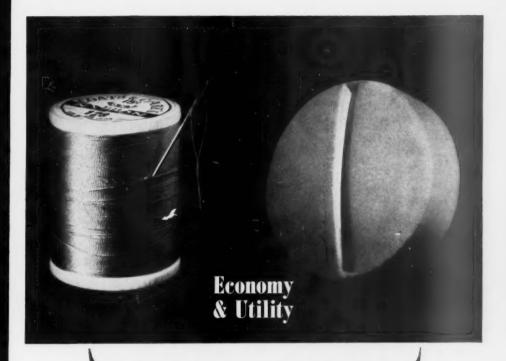
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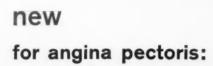
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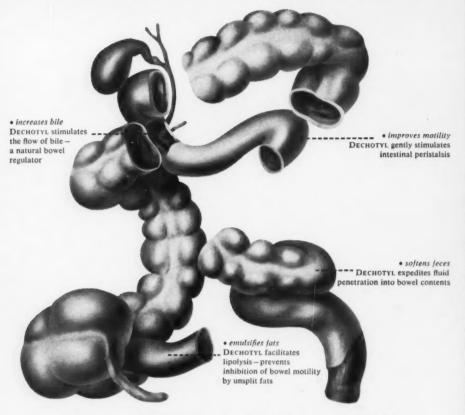


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Recommended to help convert the patient—naturally and gradually—to healthy bowel habits. Regimens of one week or more are suggested to assure maintenance of normal rhythm and to avoid the repetition of either laxative abuse or constipation.

Average adult dose: Two Trablets at bedtime as needed or as directed by a physician.

Action usually is gradual, and some patients may need 1 or 2 Trablets 3 or 4 times daily.

Contraindications: Biliary tract obstruction; acute hepatitis.

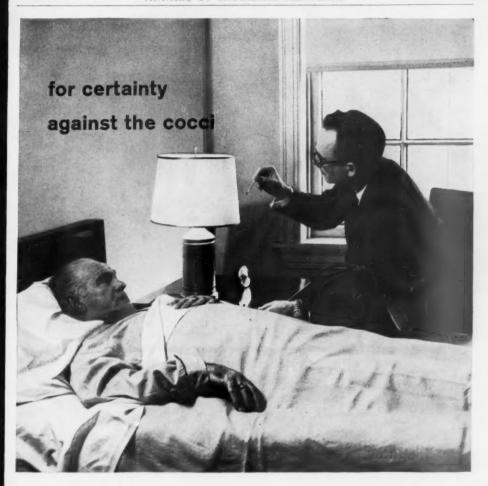
DECHOTYL TRABLETS provide 200 mg. DECHOLIN,® (dehydrocholic acid, AMES), 50 mg. desoxycholic acid, and 50 mg. dioctyl sodium sulfosuccinate, in each trapezoid-shaped, yellow Trablet. Bottles of 100.

*AMES T.M. for trapezoid-shaped tablet.

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Elipten is a new anticonvulsant chemically unrelated to other antiepileptic agents. Clinical trials in thousands of patients have shown that it controls most types of epilepsy and is especially effective when combined with other anticonvulsants.

Improves Control, Alertness, Learning Ability

With Elipten, more epileptic patients can be completely or adequately controlled. Elipten reduces the frequency of seizures in most types of epilepsy and is often effective in refractory cases, especially when combined with other anticonvulsants. Used adjunctively, it often permits reduced dosage of other drugs, thus minimizing their side effects; in some cases, other drugs can be eliminated.

By obviating or reducing the need for barbiturates, Elipten improves alertness and learning ability in children. It has little or no toxic effect on liver, kidney, or blood.

Clinical Reports

Forster' states: "Elipten... has a definite role in improving the therapy, particularly of petit mal epilepsy." He notes further that Elipten "... oftentimes will turn the tide when added to partially successful medication." Meyer2 observes: "... this drug is useful in generalized and localized convulsions as well as in status epilepticus. In addition, it is useful in the control of petit mal epilepsy and is of particular benefit in those cases where petit mal and generalized convulsions are combined. We have found it less useful in temporal lobe seizures." Lambros^a notes complete control or marked improvement in 27 of 35 patients treated with Elipten (13 were gradually switched to Elipten alone; 14 were given other anticonvulsants adjunctively). Niswander and Karacan' report that in 38 hospitalized psychotic epileptic patients given Elipten, grand mal seizures were reduced 25 to 35 per cent. Carter recommends concomitant use of Elipten and diphenylhydantoin sodium "... to enhance effectiveness and reduce the dosage of both drugs."

While most investigators report that a transient skin rash occurs in some patients, especially when initial dosage is high, Sheehan* states: "On reduction of the dose, this rash quickly disappears and does not recur when the dose is gradually stepped up to its original level." Forster¹ also notes that "... this [the rash] is not a serious complication and does not rule out Elipten therapy."

Complete information on Elipten is available on request.

SUPPLIED: Tablets, 250 mg. (white, scored); bottles of 100.

References: 1. Forster, F. M.: Wisconsin M. J. 58:375 (July) 1959. 2. Meyer, J. S.: M. Times 87:743 (June) 1959. 3. Lambros, V. S.: Dis. Nerv. System 19:349 (Aug.) 1958. 4. Niswander, G. D., and Karacan, I.: Am. J. Psychiat. 116:260 (Sept.) 1959. 5. Carter, C. H.: Dis. Nerv. System 21:50 (Jan.) 1960. 6. Sheehan, S.: Irish J. M. Sc. 390:261 (June) 1958.

ELIPTEN® (amino-glutethimide CIBA)

C I B A

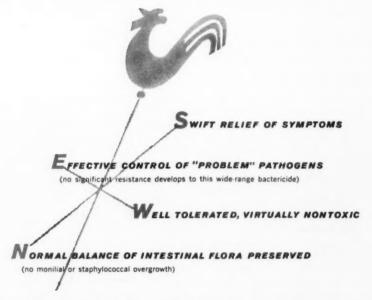
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Galeota, W.R., and Mcranville., B. A.: Student Medicine (in press)

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1. Russek, H.I.: Am. J. Cardiol. 3:547 (April) 1959.

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References:
1. Yü, T. E., Burns, J. J., and Gutman, A. B.:
Arth. & Rheumat. 1:532, 1958. 2. Gutman.
A. B., and Yü, T. F.; Bull. N. Y. Acad. Med.
34:287, 1958. 3. Kersley, G. D., Cook, E. R.,
and Tovey, D. C. J.: Ann. Rheumat. Dis.
17:326, 1958. 4. Ogryzlo, M. A., and Harrison,
J.: Ann. Rheumat. Dis. 16:425, 1957.

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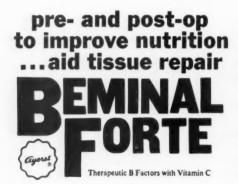


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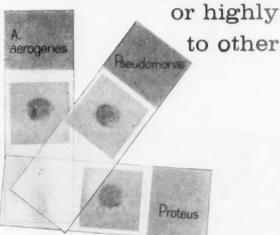
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In addition to the expected broadspectrum range of effectiveness, Declomycin has demonstrated activity against strains of Pseudomonas, Proteus and <u>A. aerogenes</u> un-

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1. Department of Clinical Investigation, Lederle Laboratories, F. M. Phillips, Director. Interim Report on Clinical and Pharmacologic Investigations. 2. Finland, M.; Hirsch, H. A., and Kunin, C. M.; Read at Seventh Annual Antibiotics Symposium, Washington, D. C., November 5, 1959. 3. Hirsch, H. A.; Kunin, C. M., and Finland, M.; München, med. Wchnschr. To be published. 4. Roberts, M. S.; Seneca, H., and Lattimer, J. K.; Read at Seventh Annual Antibiotics Symposium, Washington, D. C., November 5, 1959. 5. Vineyard, J. P.; Hogan, J., and Sanford, J. P.; Hogan, J., and Sanford, J. P.; Hogan, J., and Sanford, J. P.; Bid. Capsules, 150 mg.—Pediatric Drops, 60 mg.—Cc. Lsp.



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*Thompson, R. E., and Hecht, R. A.: Am. J. Clin. Nutrition 7:311-317 (May-June) 1959.

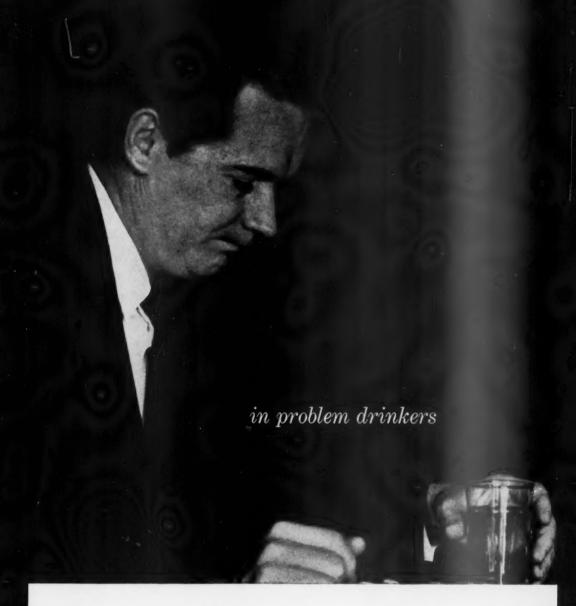
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1. Selzer, A. and Rytand, D.A.: COUNCIL ON DRUGS, Report to Council J.A.M.A. 160:762, (Oct. 11) 1958.



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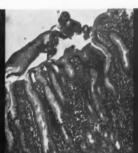
a pathological entity histologically demonstrable



NORMAL GASTRIC MUCOSA



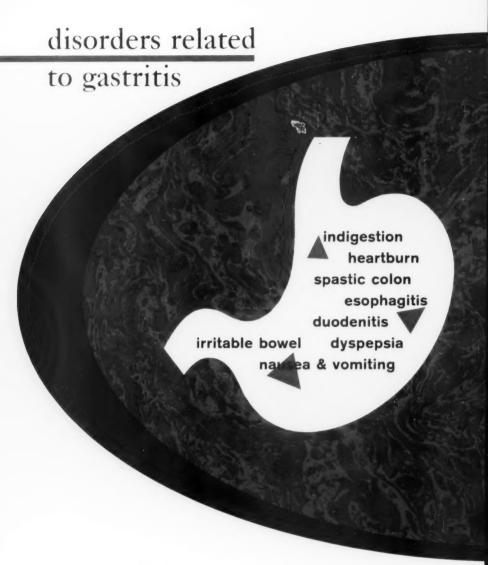
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Irreversible. Considerable distortion of glands. Mucous cells indicate conversion to colonic-type tissue, Fragmentation of mus-

Microscopic views of gastric biopsies, courtesy of E. Deutsch, M.D., originally published as part of study, Chronic Gastritis, Deutsch, E., and Christian, H. J.: J.A.M.A. 169:2012 (Apr. 25) 1959.

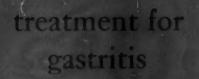


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Deutsch, E., and Christian, H.J.: J.A.M.A. 169:2012 (Apr. 25) 1959.

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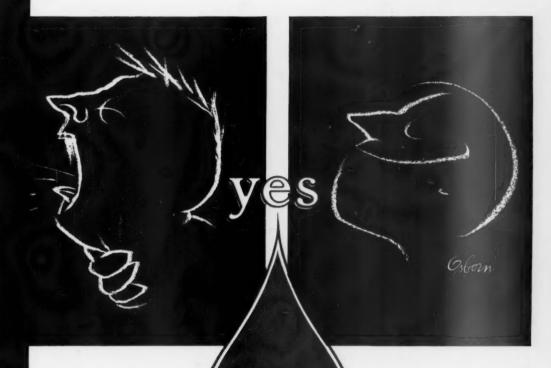
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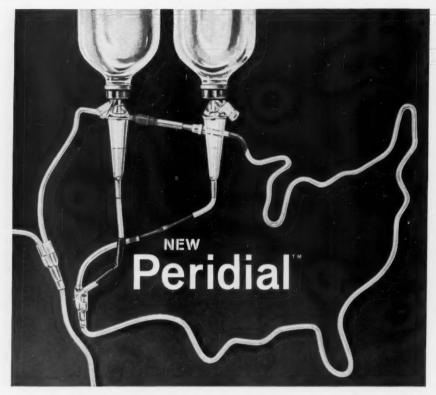
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†Maxwell, N. H., et al.: J.A.M.A. 170:917, 1959.

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Tigan

now in oral, parenteral, and suppository forms effective but not "side effective"

Tigan blocks emetic impulses at the chemoreceptor trigger zone (CTZ),1 a medullary structure activating the vomiting center. While Tigan shares with the phenothiazines the mode of antiemetic action, this is their only similarity.1 In extensive clinical studies2-14 Tigan, unsurpassed in specificity, has exhibited a virtually complete absence of side effects. Tigan has demonstrated no sedative or tranquilizing properties, no hypotensive or supramedullary effects, no extrapyramidal tract stimu-



Please Mention this Journal when writing to Advertisers

no special precautions no known contraindications

in nausea/vomiting of gastrointestinal disorders Complete or moderate relief in 78 per cent of acute or chronic gastroenteritis patients; 13 "We did not find a single toxic reaction . . . no side effects, such as sedation, skin rash . . . no changes in pulse, respiration, or . . . blood pressure." 13

in nausea/vomiting of pregnancy

No evidence of sedation or other side effects¹² observed in a series of patients of whom 94 per cent became asymptomatic on Tigan. On other antiemetic medication, several had failed to respond or had complained of drowsiness.¹²

in nausea/vomiting of radiation sickness

Protected with Tigan "... not one patient had to discontinue [deep radiation] treatments..." 5

in nausea/vomiting of drug administration

"... large intermittent dose[s] of [nitrogen mustard and other drug] therapy could be given without the associated nausea and vomiting that we had seen before."

Ilgan specific antiemetic antinauseant

no sedative properties no tranquilizer side effects

Suggested uses: Both prophylactic and therapeutic control of nausea and vomiting associated with pregnancy, travel sickness, gastrointestinal disorders, operative procedures, carcinomatoses, toxicoses, other underlying disease processes, drug administration and radiation therapy.

Dosage: Adults — 1 or 2 capsules, or ally, 2 cc intramuscularly, q.i.d. or 1 suppository, q.i.d. For children's dosage, consult literature.

In nausea and vomiting of pregnancy — Satisfactory control is usually achieved with an initial dose of two capsules immediately upon awakening. If possible, the patient should remain in bed for one-half to one hour following this dose. When nausea and vomiting are not confined to the morning hours, supplemental doses of one or two capsules should be given throughout the day at intervals of three to four hours.

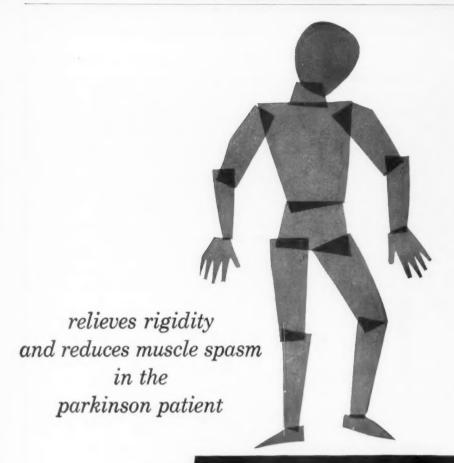
How Supplied: Tigan capsules, 100 mg, blue and white — bottles of 100 and 500. Tigan ampuls, 2 cc (100 mg/cc)—boxes of 6 and 25. Tigan Pediatric Suppositories, 200 mg, boxes of 6.

References: 1. W. Schallek, G. A. Heise, E. F. Keith and R. E. Bagdon, I. Pharmacol. & Exper. Therap., 126:270, 1959. 2. W. B. Abrams, I. Roseff, J. Kaufman. L. Goldman and A. Bernstein, to be published. 3. I. Roseff, J. Kaufmans, I. Kaufman, L. Goldman and A. Bernstein. I. Newark Beth Israel Hosp., 9:189, 1958. 4. O. C. Brandman, paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. 5. J. A. Lucinian, ibid. 6. D. W. Molander, ibid. 7. B. I. Shnider, ibid. 8. W. S. Derrick, ibid. 9. B. Wolfson and F. F. Foldes, ibid. 10. L. McLaughlin, ibid. 11. Reports on file, Roche Laboratories. 12. Personal communications. 13. W. K. Gauthier, Discussant at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. 14. H. E. Davis, ibid.

TIGAN® Hydrochloride = 4-(2-dimethylaminoethoxy)-N-(3,4,5-trimethoxybenzoyi) benzylamine hydrochloride



Division of Hoff mann-La Roche Inc. Nutley 10, N. J.



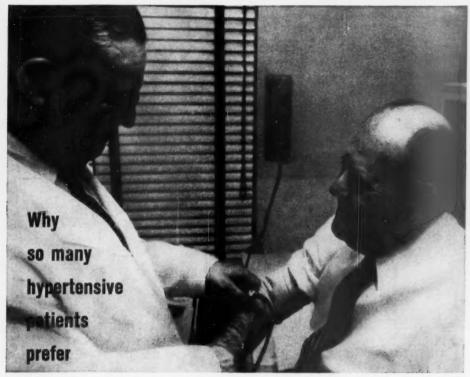
PHENOXENET A new synthetic compound

"Chlorphenoxamine (Phenoxene) exerts a gentle yet potent action . . . a muscle relaxant action also an energizing and stimulating action, without induction of excitement or agitation. Patients are able to move faster and more freely and with greater strength and longer endurance. It helps to loosen rigid muscles, and it successfully counteracts akinesia, tiredness, and weakness."*

*Doshay, L. J., and Constable, K.: Treatment of Paralysis Agitans with Chlorphenoxamine Hydrochloride, J.A.M.A. 170:37 (May 2) 1959.

A REPRINT OF THE COMPLETE ARTICLE AND CLINICAL TRIAL SUPPLIES ARE AVAILABLE ON REQUEST.





Singoserp:

It spares them from the usual rauwolfia side effects

FOR EXAMPLE: "A clinical study made of syrosingopine [Singoserp] therapy in 77 ambulant patients with essential hypertension demonstrated this agent to be effective in reducing hypertension, although the daily dosage required is higher than that of reserpine. Severe side-effects are infrequent, and this attribute of syrosingopine is its chief advantage over other Rauwolfia preparations. The drug appears useful in the management of patients with essential hypertension."*

*Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. 169:1609 (April 4) 1959.



(syrosingopine CIBA)

First drug to try in new hypertensive patients

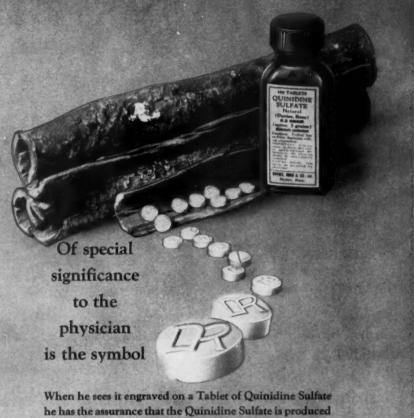
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Supplied: Singoserp Tablets, 1 mg. (white, scored); bottles of 100. Samples available on request. Write to CIBA, Box 277, Summit, N. J.

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Complete information available on request.

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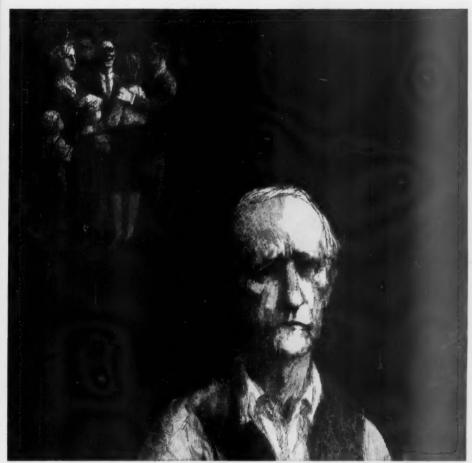
from Cinchona Bark, is alkaloidally standardized, and therefore of unvarying activity and quality.

> When the physician writes "DR" (Davies, Rose) on his prescriptions for Tablets Quinidine Sulfate he is assured that this "quality" tablet is dispensed to his patient.

> > Rx Tablets Quinidine Sulfate Natural 0.2 Gram (or 3 grains) Davies, Rose

Clinical samples sent to physicians upon their request

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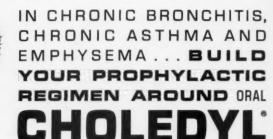


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controls anxiety and tension in everyday practice

I'm old... can't they give me more consideration ? In your practice, many agitated, senile patients can benefit from Vesprin—a full range tranquilizer with a low order of toxicity and minimal side effects. While Vesprin tranquilizes, it does not produce somnolence, and clinical trials indicate that, in patients of all ages, a wide latitude in dosages may be employed safely. Consult Vesprin package insert or PDR for indications, dosage and directions for use. Supply: for oral use—tablets containing 10, 25 and 50 mg. SQUIBB

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Choledyl, the choline salt of theophylline, improves pulmonary function, betters breathing, forestalls the crisis, is basic in any prophylactic regimen. A pure bronchodilator, Choledyl is free of sedative and sympathomimetic effects...produces higher theophylline blood levels than does oral aminophylline . . . is not likely to cause gastric irritation or drug fastness...is excellent for long-term use. Usual adult dose: 200 mg. q.i.d. [

CHILCOT



Salesman, 50 years of age, reported the following symptoms: pain, belching, abdominal distention and spasm. The patient also reported occasional mucous diarrhea and bloody stools. These symptoms had persisted for eight weeks. Barium enema studies supported the diagnosis of spastic colitis.

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On a bland, low residue diet and one 'Combid' *Spansule* capsule b.i.d., the patient became symptom-free. He was maintained on 'Combid' alone once his symptoms were under control.

'Combid' Spansule capsules reduce:

- secretion - spasm - nausea and vomiting - anxiety, tension and apprehension

for 10 to 12 hours after one oral dose.



Spansule®

brand of sustained release capsules

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ROMILAR has one specific central action: raising the cough reflex threshold.¹ There is no analgesic effect, no central depression.¹⁻⁷ Cough control begins within 15 to 30 minutes and lasts for as long as six hours.⁷ ROMILAR is a unique cough specific: it provides the antitussive potency of codeine with the safety of a placebo.³ There is no tolerance liability, no addictive potential.^{1,3-8}

ROMILAR is of special value when cough suppression is vital—in patients with pulmonary and cardiac disease, hernia or rib fracture, before and after abdominal and EENT surgery and during i.v. infusions.

SUPPLY: Syrup in bottles of 4 oz, 16 oz, 1 gal. Tablets in bottles of 20, 100, 500. Expectorant in bottles of 16 oz, 1 gal.

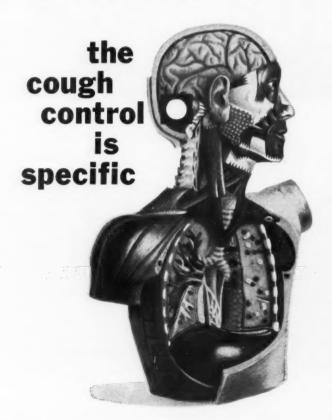
REFERENCES: 1. H. A. Bickerman in W. Modell, Ed., Drugs of Choice 1958-1959, St. Louis, The C. V. Mosby Company, p. 557. 2. L. J. Cass and W. S. Frederik, New England J. Med., 249:132, 1953. 3. L. J. Cass, W. S. Frederik and J. B. Andosca, Am. J. M. Sc., 227:291, 1954. 4. H. Isbell and H. F. Fraser, J. Pharmacol. & Exper. Therap., 107:524, 1953. 5. W. M. Benson, P. L. Stefko and L. O. Randail, J. Pharmacol. & Exper. Therap., 109:189, 1953. 6. New and Nonofficial Drugs 1959, Philadelphia, J. B. Lippincott Company, 1959, p. 326. 7. N. Ralph, Am. J. M. Sc., 227:297, 1954. 8. H. A. Bickerman, E. German, B. M. Cohen and S. E. Itkin, Am. J. M. Sc., 234:191, 1957.

Romilar

NON-NARCOTIC COUGH SPECIFIC WITH PROMPT, PROLONGED ACTION



ROCHE LABORATORIES . Division of Hoffmann-La Roche Inc . Nutley 10, N. J.



announcing a new class of drug/the first analgomylaxant



analexinal eximation of the second of the se

a single chemical that is both a general non-narcotic analgesic and an effective muscle relaxant

announcing a new class of drug

therefore...in pain... where pain makes tension and tension makes pain... analexin stops both effectively

Analexin is a new synthetic chemical (phenyramidol hydrochloride) that inherently possesses within one molecular structure two different pharmacologic actions: (1) general analgesia, by raising the pain threshold and thus decreasing the perception of pain, and (2) muscle relaxation, by selectively depressing subcortical, brain stem and spinal polysynaptic transmission (interneuronal blockade), abolishing abnormal muscle tone without impairing normal neuromuscular function.^{1,2}

Although the analgesic potency of one tablet is clinically equivalent to one grain of codeine, Analexin is not narcotic or narcotic related. It is not habituating and tolerance to the drug has not been noted. Muscle relaxant action is comparable to the most potent muscle relaxants available for oral use. The total effect is "analgomylaxation"—a new advance for the relief of pain.

The full chemical name for phenyramidol is 2-(\(\beta\) hydroxyphenethylamino)-pyridine hydrochloride. It is unrelated to any currently available analgesic or muscle relaxant compound. 3.4

analexin provides effective relief of the total pain experience...

The end result of pain, regardless of its origin, is discomfort or suffering paralleled by muscle tension. Thus muscle tension may play a fundamental role in the total pain experience even though it does not initiate the pain. Employment of a single agent that produces two distinct but associated physiologic responses has obvious advantages, for relief of the total pain experience is better accomplished by the integrated action of phenyramidol which acts on both pain centers and muscle to produce analgesia and relieve muscle tension simultaneously.

with remarkably few side effects

Side effects such as sedation, euphoria, mental confusion and depression, sometimes associated with interneuronal blocking and certain analgesic agents have not been noted with Analexin. Incidence of reactions is low and those reactions that occasionally occur (such as gastric irritation and pruritus) are of a mild and transient nature and do not limit therapy.

announcing a new class of drug

results with analexin in clinical trials

Batterman, Grossman and Mouratoff' compared Analexin with aspirin, sodium salicylate and a placebo in a series of 195 patients with various painful conditions. The authors concluded:

"Not only is satisfactory relief of painful states achieved in the majority of patients regardless of etiology and duration of pain, but there is also no evidence suggestive of cumulative toxicity. Furthermore, in contrast to codeine and meperidine, the likelihood of untoward reactions occurring in ambulant patients is not high. This is a decided advantage since the control of pain in the ambulant patient with chronic pain is a major clinical problem."

"Phenyramidol (Analexin), with therapeutic doses is not only safe for chronic administration, but also to date we have noted no adverse effect upon the cardiovascular, gastrointestinal, respiratory, kidney, liver or central nervous systems."

Wainer reported a series of 200 cases treated with phenyramidal for various painful conditions. In fifty of these patients who had dysmenorrhea, he saw excellent results in 40, good results in 5 and poor results in 5. Further examination in 4 cases not responding revealed presence of organic pathology. A second group of 50 cases with headache and associated premenstrual tension responded with over-all excellent results. Wainer also reports the use of phenyramidal to replace codeine for postpartum pain and describes 100 cases wherein a combination of phenyramidal with aluminum aspirin (Analexin-AF) successfully replaced aspirin and codeine therapy.

more results with analexin in clinical trials

A In another series of dysmenorrhea cases, Bader² compiled data on 20 employees of a telephone company who required ½ to 2 days off from work every month regardless of prior therapy employed. Satisfactory results were achieved in 15 out of 20 and a fair response in the remaining five. All were able to remain on the job although relief was not complete in the latter cases.

Bealer⁸ treated 32 patients with phenyramidal mostly for musculoskeletal disorders and had good or very good results in 15, fair results in 14 and poor or inconclusive results in 2 patients. Cohen' used phenyramidal together with aspirin in 15 patients with such conditions as sciatic pain, osteoarthritis, anterior chest wall syndrome, etc. and got outstanding relief in 80 per cent. Gilbert 10 reported that 15 patients with nonspecific headache had excellent relief in a matter of minutes with phenyramidal, and in 8 cases of dry socket pain Bruno¹¹ reports immediate relief in six cases and good results later in the other two after sockets were curetted under local anesthesia. Stern¹² reported on 40 ambulatory cases with a variety of painful conditions and saw good relief in 32 patients and poor in 8. Results were best in acute sacroiliac pain, myositis, muscle spasm, fractures, pleurisy and neuritis. Ten of 13 patients with osteoarthritis responded very well and are continuing on phenyramidal therapy.

announcing a new class of drug

analexin (phenyramidal)

for relief of pain and muscle tension in: low back pain sprains and strains myalgia glass arm wry neck osteoarthritis dysmenorrhea tension headache gout postpartum pain epigastric distress

(pylorospasms, gastritis, duodenal ulcer, cholecystitis) genitourinary conditions

(premenstrual cramping or tension) abdominal distres (flatulence, colic) toothache and dry sucket pain

analexin-AF (phenyromidal with aluminum aspirin)

for relief of pain and muscle tension also involving inflammatory processes and/or fever, as in: arthritis arthralgia bursitis tendinitis myolgia of strain and tear pre- and postoperative toothache

dosage:

analexin: for relieving pain and/or muscle tension, one or two tablets every 4 hours. In dysmenorrhea, two tablets initially then one tablet every 2 to 4 hours as needed.

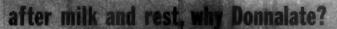
analexin-AF: two tablets every 4 hours or as required.

supply:

analexin tablets—Each tablet contains 200 mg. of phenyramidal HCI. Bottles of 100 tablets.

analexin-AF tablets - Each tablet contains 100 mg. of phenyramidal HCl and 300 mg, of aluminum aspirin. Bottles of 100 tablets.

REPRINTEDES: 1. O'Doll, T. B.; Wilson, L. R.; Niepell, M. D.; White, M. D., and Mirsky, J. H.; J. Phermocol. & Exper. Therap., in press. 2. O'Doll, T. B.; Wilson, L. R.; Nepell, M. D.; White, H. D., and Mirsky, J. H.; Fed. Proc. 18:1694, 1959. 3. Gray, A. R. and Heitmeier, D. E.; J. Am. Chom. Sec. 81:4347, 1959. 5. Bottomman, R. C.; Grossman, A. J., and Mouratelf, G. J.; Am. J. Med. Sc. 238:315, 1959. 6. Walner, A. S.; The Use of Phenyramidal in Obstetries and Gynocology. Read before the New York Academy of Sciences, Dec. 5, 1959. 7. Beder, G.; Clinical Report 511; 596. 8. Beder, J. D.; Clinical Report 511; 592. 9. Cohen, B. M.; Clinical Report 511; 596. 10. Gilbert, E.; Clinical Report 511; 597. 11. Brone, E. A.; Clinical Report 511; 593. 12. Stern, E.; Clinical Report 511; 599.



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Donnalate

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anticholinergic
KEEPS
THE STOMACH
FREE OF PAIN

tranquilizer

KEEPS

THE MIND OFF

THE STOMACH



Milpath acts quickly to suppress hypermotility, hypersecretion, pain and spasm, and to allay anxiety and tension with minimal side effects.

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Milpath

*Miltown +anticholinergic

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children won't hide from this ORAL PENICILLIN with INJECTION PERFORMANCE

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PEN VEE K

Liquid: Penicillin V Potassium for Oral Solution, Wyeth

Tablets: Penicillin V Potassium, Wyeth Wyeth Laboratories, Philadelphia 1, Pa.



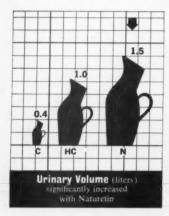
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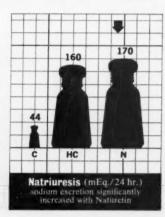
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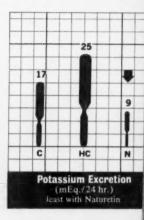
Naturetin Squibb Benzydroflumethiazide

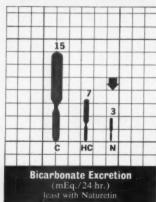
"When compared to other members or this heterocyclic at of compounds, this drug [NATURETIN] shows a significantly creased natriuresis and decreased loss of potassium and bi bonate. In this respect it more closely approaches a natura 'ideal diuretic.' It is effective upon continuous administration causes no significant serum biochemical changes. It is effec in a wide variety of edematous and hypertensive states represents a significant advance in diuretic therapy." Ford, I Pharmacological observations on a more potent benzothiadia diuretic; accepted for publication by the American Heart Iou

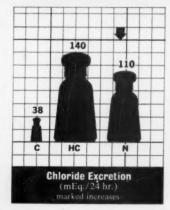
Comparison of electrolyte excretion pattern for the 24 hours followitypical doses of chlorothiazide, hydrochlorothiazide, and Natureti













Typical Doses: Chlorothiazide-1,000 mg.; Hydrochlorothiazide-50 mg.; Naturetin (Benzydroflumethiazide)-5 m

1. Adapted from: Ford, R. V., Squibb Clin. Res. Notes 2:1 (Dec.) 1

A single 5 mg. tablet once a day provides all these advantages²

prolonged action — in excess of 18 hours
convenient once-a-day dosage
low daily dosage — more economical for the patient
no significant alteration in normal electrolyte excretion pattern
repetitively effective as a diuretic and antihypertensive
greater potency mg. for mg.—more than 100 times as potent as chlorothiazide
potency maintained with continued administration
low toxicity — few side effects — low salt diets not necessary
comparative studies with chlorothiazide, hydrochlorothiazide, and Naturetin
disclose that smallest doses of Naturetin produce greater weight loss per day
in hypertension, Naturetin, alone or in combination with other antihypertensives, produces significant decreases in mean blood pressure
and other favorable clinical effects

purpura and agranulocytosis not observed allergic reactions rarely observed

Paperts (1950) to the Southh Institute for Madical Research

the premenstrual syndrome, nephrosis and nephritis, cirrhosis with ascites, edema induced by drugs ertain steroids); in the management of hypertension, used alone, combined with Raudixin (Squibb anwolfa Serpentina Whole Root), or with other antihypertensive drugs, such as ganglionic blocking agents. patraindications: none, except in complete renal shutdown.

recautions: when Naturetin is added to an antihypertensive regimen including hydralazine, ratrum, and/or ganglionic blocking agents, immediate reduction must be made in the dosage for all eparations; the dosage for ganglionic blocking agents must be decreased by 50% to avoid a precipitous op in blood pressure. This also applies if these hypotensive drugs are added to an established Naturetin gimen . . . in hypochloremic alkalosis with or without hypokalemia . . . in cirrhotic patients or those on italis therapy when reductions in serum potassium are noted . . . in diabetic patients or those edisposed to diabetes . . . when increased uric acid concentrations are noted . . . when signs — g or abdominal cramps, pruritus, paresthesia, rash — suggestive of hypersensitivity, are noted.

turētin — Dosage: in edema, average dose, 5 mg., once daily, preferably in the brning; to initiate therapy, up to 20 mg., once daily or in divided doses; for intenance, 2.5 to 5.0 mg., daily in a single dose. In hypertension: suggested tial dose, 5 to 20 mg. daily; for maintenance, 2.5 to 15 mg. daily, depending the individual response of the patient. When Naturetin is added to an anti-pertensive regimen with other agents, lower maintenance doses of each ug should be used.

turetin - Supplied: tablets of 2.5 mg. and 5 mg. (scored).

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Squibb Quality-

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DIEM - AND 'NATURETIN' ARE SQUIDS TRADEMARKS

SAFER.

MORE EFFICIENT

BETTER TOLERATED

b.i.d. dosage

QUINIDINE

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IN CARDIAC

ARRHYTHMIAS



Safer and more efficient because there is no let-down in plasma levels where arrhythmias tend to recur. Better tolerated because quinidine gluconate is ten times as soluble as quinidine sulfate—and so is easier on the g.i. tract. Quinaglute Dura-Tab S.M. every 12 hours maintains uniform, effective plasma levels around the clock.

PAGE 893

QUINAGLUTE DURA-TAB'S.M.

A quinidine of choice in atrial fibrillation, flutter, premature contractions, auricular tachycardia.

DOSAGE: for conversion of auricular fibrillation to normal sinus rhythm, in most cases, 2 Quinaglute Dura-Tab S.M. tablets 3 to 4 times a day, for 2 to 3 days; longer periods are required in some patients...for maintenance 1 to 2 tablets every 10 to 12 hours. Bottles of 30, 100 and 250.

- Bellet, S.; Finkelstein, D., and Gilmore H.: A.M.A. Archives Int. Med. 100:750, 1957.
- 2. Bellet, S.: Amer. Heart J. 56:479, 1958.
- 3. Finkelstein, D.: Penn. Med. J. 61:1216, 1958.

exclusive oral Sustained Medication*
Quinidine Gluconate (5 gr.)

for samples and literature write . . .

WYNN PHARMACAL CORPORATION

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also available:

INJECTABLE QUINAGLUTE 10 cc. Multiple Dose Vials, 0.08 Gm. Quinidine Gluconate per cc.

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in pain, such as that of cancer, Thorazine°,

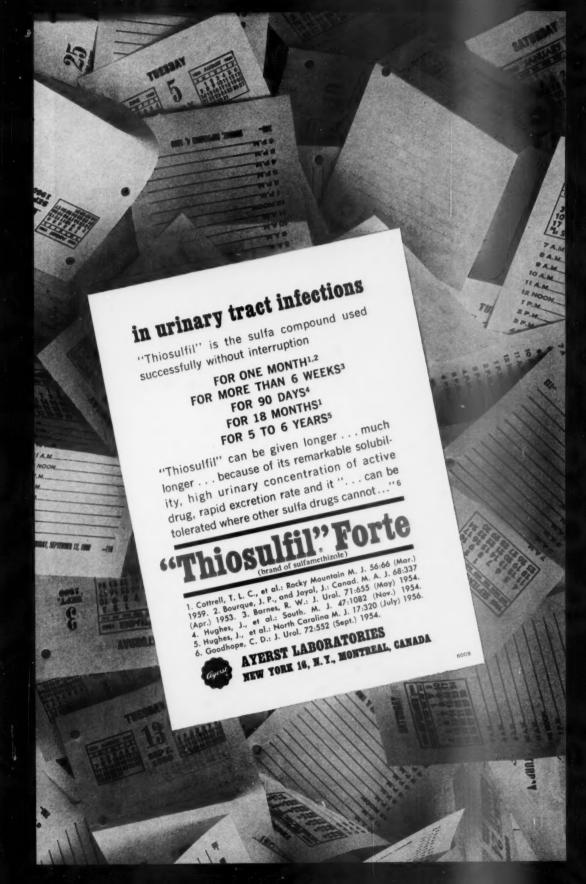
brand of chlorpromazine

one of the fundamental drugs in medicine, reduces by potentiation the amount of narcotic needed; alleviates the anxiety that intensifies suffering; improves the patient's mental outlook. Also, controls nausea and vomiting.



SMITH KLINE & FRENCH





RECOVERY RATE: OVER 90% in over 1,000 published cases of thromboembolic disease . at present, this is the oral anticoagulant of choice." - noncumulative - Rapid in action

- rapid in action

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of ambulatory patients

Lafe and effective anticoagulant

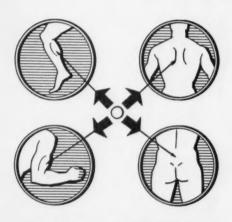
for long-term use..."2 50 mg. ALKER LABORATORIES.

HEDULIN is the trademark for the Walker brand of phenindione. 50 mg. scored tablets for therapeutic use; 20 mg. scored tablets for prophylactic use. Bottles of 100 and 1,000. For more detailed information and a clinical trial supply of Hedulin, write to Walker Laboratories, Inc., Mount Vernon, N. Y.

1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.

For Dependable Relief of Skeletal Muscle Spasm...

Two Tablets Per Day



INDICATED IN ALL TYPES OF ACUTE MUSCLE SPASM following sprains, strains, whiplash injuries, intervertebral disc syndrone, chronic osteoarthritis, etc.

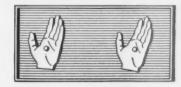
 $Norfleec{x}$ for prompt, safe

ADVANTAGES

- · Mobility is restored quickly and associated pain relieved by prompt relaxation of muscle spasm.
- · Prolonged action and potency provide round-the-clock benefits-including uninterrupted sleep.
- Impairment of general muscle tonus has not been reported when the recommended standard dosage is followed.

STANDARD DOSAGE Only one tablet b.i.d. for all adults regardless of age, weight, or sex. Simple dosage assures maximum patient cooperation.

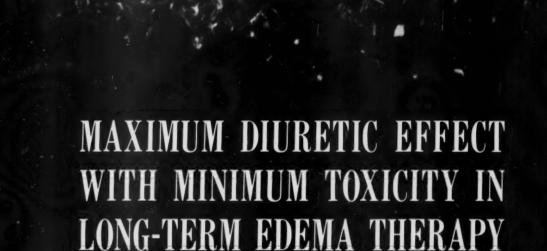
spasmolytic action





Northridge, California

confirmed in clinical study:



ORETIC

a potent means when the end is diuresis





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many cases

ORETIC

diets

Studying **ORETIC**, which they describe as "... a significant advance in development of diuretic agents of greater potency without increasing toxicity..." the investigators tested, among other properties of the compound, its clinical efficiency in long-term treatment of various edematous conditions.

Twenty patients were studied: eleven cardiacs, 3 nephrotics, 2 cirrhotics, 2 pregnancies (third trimester) and 2 "steroid" edematous patients.

Drug was given in 50-mg. dosages, daily for ninety days. Observations were made in the control state, and on the seventh, twenty-first and ninetieth days. Results were computed for body weight, serum electrolytes, blood urea, nitrogen and hematocrit:

CLINICAL RESPONSES TO ORETIC IN VARIOUS EDEMATOUS STATES

(Average Values for Each Group, Dose of 50 mg. daily)

| Type of Edema | Number of pts. | Period | Cumulath Weight | .6 | Serum (mEq/L) | | | | |
|------------------|----------------|---------|--------------------|-----|---------------|-----------------|-----|------------|------|
| | | | Loss (lbs.) | Na | K | CO ₁ | CI | BUN mg% | нст. |
| Cardiac | 11 | Control | | 139 | 4.4 | 27 | 107 | 20 | 44 |
| | | Day 7 | 4 | 138 | 4.2 | 29 | 104 | 22 | 45 |
| | | Day 21 | 9 | 136 | 4.1 | 30 | 103 | 23 | 46 |
| | | Day 90 | 14 | 137 | 4.2 | 30 | 104 | 25 | 48 |
| Nephratic | 3 | Control | | 132 | 3.6 | 24 | 93 | 32 | 41 |
| | | Day 7 | 5 | 128 | 3.5 | 26 | 91 | 30 | 42 |
| | | Day 21 | 13 | 125 | 3.3 | 27 | 90 | 29 | 44 |
| | | Day 90 | 19.5 | 127 | 3.3 | 28 | 90 | 27 | 45 |
| Cirrhotic | 2 | Centrel | | 131 | 3.2 | 26 | 88 | 9 | 39 |
| | | Day 7 | 6 | 130 | 2.7 | 25 | 86 | 10 | 42 |
| | | Day 21 | 15 | 128 | 2.6 | 26 | 85 | 11 | 41 |
| | | Day 90 | 22 | 128 | 2.7 | 26 | 84 | 10 | 42 |
| Pregnancy | 2 | Control | | 144 | 4.2 | 27 | 106 | . 11 | 40 |
| | | Day 7 | 2 | 143 | 4.1 | 28 | 102 | 13 | 41 |
| | | Day 21 | 5 | 142 | 4.1 | 31 | 99 | 13 | 43 |
| "Steroid" | 2 | Control | | 146 | 3.5 | 32 | 94 | 14 | 38 |
| | | Day 7 | 3 | 145 | 3.3 | 33 | 89 | 15 | 42 |
| | | Day 21 | 6 | 143 | 3.0 | 33 | 87 | 17 | 43 |
| | | Day 90 | 9 | 142 | 3.1 | 34 | 88 | 17 | 43 |

*Co2CP-Carbon Dioxide combining power

THE INVESTIGATORS SAID:

"The drug was effective in the therapy of edema, regardless of etiology, as seen from the data . . . All the groups had significant weight loss with the greatest loss occurring in the nephrotic and cirrhotic groups: except for the relief of the edema in all the patients observed, no other changes in clinical status were observed. Persistence of diuresis and the lack of additional toxicity in long term (90 days) therapy has been observed."

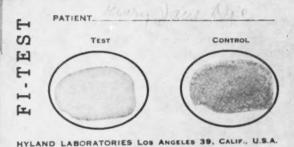
ORETIC, indicated for hypertension and edema, is supplied in 25- and 50-mg. tablets, bottles of 100 and 1000.

ABBOTT

Bibliographical Note: The study quoted has been published in the Sept., 1959, issue of Current Therapeutic Research, pp. 26-33.

NEW

RAPID SCREENING TEST FOR HYPOFIBRINOGENEMIA



FI-TEST*

Test results at patient's bedside – from skin puncture to reading – in less than 2 minutes. Only one drop of blood required. Test performed by simple, rapidslide technic.

FI-TEST indicates whether fibrinogen content is above or below 100 mg-%, the concentration considered critical. Easy-to-read results indicate promptly whether or not replacement fibrinogen is needed. (If reading shows a normal fibrinogen level, needless replacement therapy may be avoided and the physician is alerted to seek another explanation for continued bleeding.)

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a you prescribe POLANIL (composed DLARAMINE®, today's lowest-dosage istamine, plus DERONIL®, today's lowest-e corticosteroid), you can control the disport of allergic dermatoses, hay fever and season of the control of the corticosteroid.

e corticosteroid), you can control the disort of allergic dermatoses, hay fever and seasonal
na. (Remember, too, POLARAMINE alone or in combination
ols discomfort of seasonal and nonseasonal allergies; allermplications of respiratory illness; drug and serum reactions,
use of its unique composition, POLANIL is particularly
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may not be fully effective, or for which full steroid

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POLANIL is effective in treating patients with resistant allergic dermatoses and seasonal asthma because the POLARAMINE component blocks the reception of histamine in precisely those areas where histamine is concentrated and where it provokes the most intense reaction: the skin, the upper gastrointestinal tract and the respiratory tree. The DERONIL component possesses an intensified anti-inflammatory activity with minimal effect on electrolyte and water balance. Dosage: One or two tablets after meals and at bedtime. Dosage should be gradually reduced to lowest effective maintenance level or, if possible, discontinued. Supply: Available in bottles of 50. Each tablet contains 0.25 mg. dexamehasone, 2 mg. dexchlorpheniramine maleate, and 75 mg. ascorbic acid.

POLANIL in almost all cases even

when edema and erythema may persist.

another patient with hypertension?



indicated in all degrees of hypertension

effective by itself in most hypertensives

HYDROPRES.

HYDRODIURIL" with RESERPINE

HYDROPRES can be used:

- ▶ alone (In most patients, HYDROPRES is the only antihypertensive medication needed.)
- as basic therapy, adding other drugs if necessary (Should other antihypertensive agents need to be added, they can be given in much lower than usual dosage so that their side effects are often strikingly reduced.)
- as replacement therapy, in patients now treated with other drugs (In patients treated with rauwolfia or its derivatives, HYDROPRES can produce a greater antihypertensive effect. Moreover, HYDROPRES is less likely to cause side effects characteristic of rauwolfia, since the required dosage of reserpine is usually less when given in combination with HydroDIURIL than when given alone.)

HYDROPRES-25

25 mg. HydroDIURIL, 0.125 mg. reserpine. One tablet one to four times a day.

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50 mg. HydroDIURIL, 0.125 mg. reserpine. One tablet one or two times a day.

If the patient is receiving ganglion blocking drugs or hydralazine, their dosage must be cut in half when HYDROPRES is added.

For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.



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once each week

burns
debility
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Durab

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- + positive anabolic gains
- + marked sense of well-being
- + direct control of your patient
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One injection of DURABOLIN each week often induces a marked sense of well-being in the asthenic, undernourished, or "run-down" patient. Outlook and appetite improve. Sustained, positive nitrogen balance is established. Solid muscular tissue develops. Weight is gained without edema. The safest and most potent tissue-building agent, DURABOLIN is also the easiest to use and most economical. The physician injects it each week. There can be no unfilled prescription, no forgotten dose. Progress is observed directly. Adults: 25 mg. (1 cc.) i.m. weekly, or 50 mg. (2 cc.) every second week. Children: half adult dosage. Organon Inc., Orange, N. J.





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In the treatment of depression Tofrānil has established the remarkable record of producing remission or improvement in approximately 80 per cent of cases.¹⁻⁷

Tofrānil is well tolerated in usage—is adaptable to either office or hospital practice—is administrable by either oral or intramuscular routes.

Tofrānil...a potent thymoleptic ...not a MAO inhibitor. Does act effectively in all types of depression regardless of severity or chronicity.

Does not inhibit monoamine oxidase in brain or liver; produce CNS stimulation; or potentiate other drugs such as barbiturates and alcohol.

Detailed Literature Available on Request.

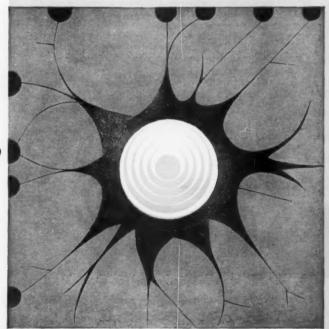
Tofrānil® (brand of imipramine HCl), tablets of 25 mg., bottles of 100. Ampuls for intramuscular administration only, each containing 25 mg. in 2 cc. of solution, cartons of 10 and 50.

References: 1. Ayd. F. J., Jr.: Bull. School Med., Univ. Maryland 44:29, 1959. 2. Azima, H., and Vispo, R. H.: A. M. A. Arch. Neurol. & Psychiat. 81:658, 1959. 3. Lehmann, H. E.; Cahn, C. H., and de Verteuil, R. L.: Canad. Psychiat. A. J. 3:155, 1958. 4. Mann, A. M., and MacPherson, A. S.: Canad. Psychiat. A. J. 4:38, 1959. 5. Sloane, R. B.: Habib, A., and Batt, U. E.: Canad. M. A.J. 80:340, 1959. 6. Straker, M.: Canad. M. A.J. 80:346, 1959. 7. Strauss, H.: New York J. Med. 59:2906, 1959.

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in 80 per cent of cases

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DRUG-INDUCED EXTRAPYRAMIDAL DISORDERS

parkinsonism — dyskinesia — akathisia

MUSCULAR SPASTICITY NOT RELATED TO PARKINSONISM

ACTION

Frequently diminshes akinesia, rigidity, and tremor with subsequent improvement in coordinated movement, gait, and posture. Masklike face disappears. Salivation and oily skin are decreased. Oculogyric crises are often lessened in intensity and frequency.

SIDE EFFECTS

Minimum (mainly dry mouth or blurred vision).

DOSAGE

Individual adjustment of dosage is necessary in all instances. Dose range extends from 2 mg. to 24 mg. daily, in divided doses.

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Supplied as the hydrochloride salt, 2 mg. bisected tablets, bottles of 100 and 1000.

Complete information furnished upon request.

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Tablet Maalox: 0.4 Gram (equivalent to one teaspoonful), Bottles of 100.

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Samples on request.

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CALURIN is less likely to cause local irritation of the gastric mucosa... or produce chemical erosion or erosive gastritis as insoluble, acid aspirin often does. 2-11 CALURIN is freely soluble... acts faster and is more readily absorbed, producing higher initial fasting blood levels 2 than a comparative dose of aspirin.

Each Calurin tablet is equivalent to 300 mg. (5 gr.) of acetylsalicylic acid.

References 1. Wind Gastric Damage, Scientific Fublit, A.M.A. Convention, Milandic City, M. J., June 9-12, 1959. 2. Waterson, A. P.: Brit. M.J. 2.1531, 1955. 3. Editorial Comments. The effect of acetylsalicytic acid on the gestre muscas. Name A. Brit. M.J. 2.7, 1955. 3. Mair. A. and Ceasar. I.A. A. Brit. M.J. 2.7, 1955. 3. Mair. A. and Ceasar. I.A. A. Brit. M.J. 2.7, 1955. 3. Mair. A. and Ceasar. I.A. Brit. M.J. 2.7, 1955. 3. Mair. A. and Ceasar. I.A. Brit. M.J. 2.7, 1955. 3. Mair. A. and Linott, S. A. Mair. A. Brit. M.J. 2.7, 1955. 3. Mair. A. Mair. Mair. A. Mair. M. Mair.



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It's available in two forms, liquid and powder, but most adults prefer the mild tasting powder. It dissolves instantly in milk, water or juices. It promotes aciduric flora in the lower bowel which helps restore normal function. Long term treat-ment produces no side effects. Diabetic patients should allow for 60 calories for each tablespoonful.

Hootnick(1) reports, "Stools became soft in all patients and, within one week, bowel evacuations were accomplished with ease. Most patients liked the taste of the product, and the majority of them reported a feeling of well-being."

Cass and Frederik (2) also found that "Malt Soup Extract produced soft, easily evacuated stools without any side effects in constipated elderly patients."

Marshall(8) found it "a simple but highly effective treatment for chronic constipa-tion in patients of all ages."

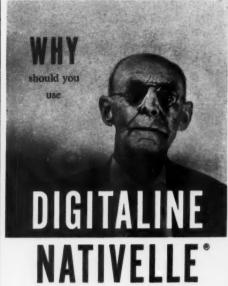
Dose: 2 tablespoonfuls twice a day. Available, liquid and powder, 8 ounce and 16 ounce bottles, at pharmacies.

Send for clinical samples (1) Hootnick, H. L.: Jnl. Amer. Ger. Soc., 4:1021-1030, 1956. (2) Cass, L. J. and Frederik, W. S.: Jnl. Lancet, 73: 414-416, 1953. (3) Marshall, W.: So. Dak. J. Med. & Pharm. 8:151:153, 1955.

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Flexibility of Administration-Digitaline Nativelle provides for rapid oral digitalization within a convenient range of tablet strengths. When desired the intravenous route, or the new intramuscular injection may be employed. The essentially non-alcoholic intramuscular formula, unlike most alcoholic menstrua, is virtually painless.

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Preludin brand of phenmetrazine hydrochloride

Through the potent appetitesuppressant action of Preludin, the success of anti-obesity treatment becomes more assured—adherence to diet becomes easier—discomfort from side reactions is unlikely.

In Simple Obesity
Preludin produces 2 to 5 times
the weight loss achievable by
dietary instruction alone. 1,2

In Pregnancy
Weight gain is kept within
bounds, without danger to
either mother or fetus.³

In Diabetes
Insulin requirements are not increased; they may even decrease as weight is lost. 4

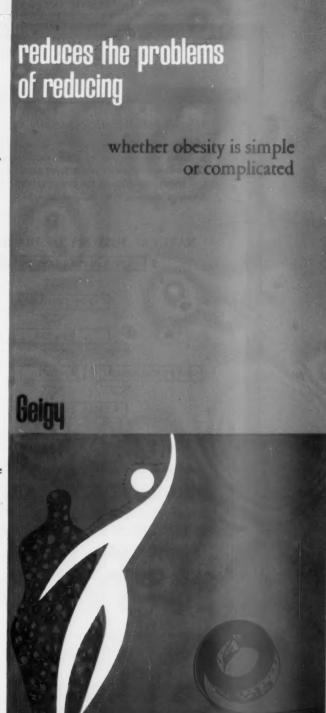
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Preludin is well tolerated and blood pressure may even fall as weight is reduced.

Patients taking Preludin usually experience a mild elevation of mood conducive to an optimistic and cooperative attitude, thereby counteracting the lassitude otherwise resulting from a reduced caloric intake. Thus, consistent weight loss over a prolonged period becomes more assured.

Preludin® Endurets^{T.M.} (brand of phenmetrazine hydrochloride), prolongedaction tablets of 75 mg. for once daily administration; and scored, square, pink tablets of 25 mg. for b.i.d. or t.i.d. administration.

Under license from C. H. Boehringer Sohn, Ingelheim Reference: (1) Barnes, R. H.: J.A. M.A. 166:898, 1958. (2) Ressler, C.: J.A. M.A. 166:898, 165:135, 1957-(3) Birnberg, C. H., and Abithol, M. M.: Obst. & Gynec. 17:463, 1958. (4) Robillard, R.: Canad. M.A.J. 76:938, 1957.

Geigy, Ardsley, New York



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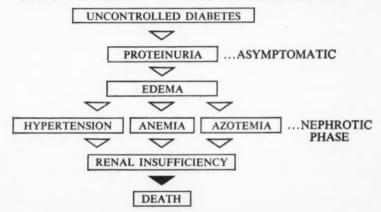
CLINICAL BRIEFS FOR MODERN PRACTICE

Why is the diabetic especially vulnerable to nephropathy?

Because the kidney is the body organ most susceptible to alteration in structure and function by the diabetic state. Seventy-five per cent of all deaths due to diabetes result from cardiovascular-renal complications. Of this group, one-fifth of the complications are primarily renal in origin.

Source: Whitehouse, F. W.: Postgrad. Med. 24:54, 1958.

NATURAL HISTORY OF DIABETIC NEPHROPATHY



Adapted from Whitehouse, F. W.: op. cit.

CHECK THE DIABETIC FOR GLYCOSURIA... AND PROTEINURIA
PROBABLY THE BEST SINGLE INDICATOR OF RENAL DISORDER

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colorimetric "dip-and-read" combination test for protein and glucose in urine

1 DIP...10 SECONDS...2 RESULTS

- · unaffected by turbidity, drug metabolites or other urine constituents
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how does Mellaril differ from other potent tranquilizers?

Mellaril

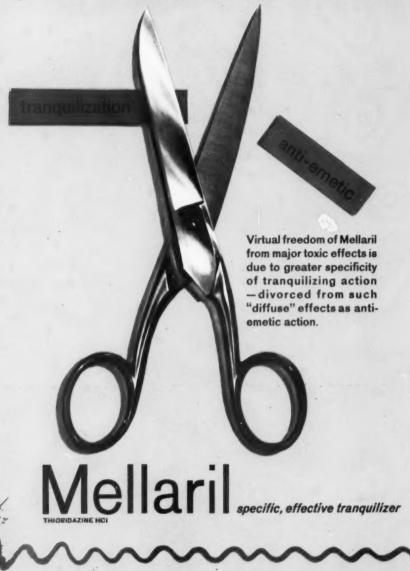
provides highly effective tranquilization, relieves anxiety, tension, nervousness,

but is virtually free of such toxic effects as



jaundice
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blood dyscrasia
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greater specificity of tranquilizing action results in fewer side effects



"Thioridazine [Mellaril] is as effective as the best available phenothiazine, but with appreciably less toxic effects than those demonstrated with other phenothiazines....This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."*

Supply: MELLARIL Tablets, 10 mg., 25 mg., 100 mg.



Tetraeycline Phosphate Complex (TETREX®)

in the Therapy of

ACUTE PHARYNGITIS, ESPECIALLY WITH LYMPHADENITIS

Ideally, selection of the proper antibiotic for treatment of acute pharyngitis should await the laboratory reports on the susceptibility of the infecting bacteria. But the busy practitioner who sees many patients a day during the upper respiratory infection season may sometimes find it difficult to avoid the empirical choice of an antibiotic. Unfortunately, this practice may sometimes result in therapeutic failure.

No matter what the pressure of the immediate situation, it is worthwhile to consider taking a bacterial specimen from the infected pharynx for culture and sensitivity studies before starting treatment. Thus, a rational basis will be provided for changing the antibiotic should the first choice prove ineffective.

Which Antibiotic?

All other things being equal, the drug of choice is the one to which the pathogen is most susceptible. But if the exigencies of the situation force the physician to a prompt use of antibiotic, a broad-spectrum preparation that produces immediate high blood levels (e.g., tetracycline phosphate complex, TETREX) probably has the best chance of controlling the pathogen.

Later, the laboratory report frequently may indicate that any one of several antibiotic agents would be equally effective against the particular microorganism in question. In such a case other factors such as frequency and severity of side effects, sensitizing potential and toxicity should be considered.

If the acute pharyngitis in question should be due to gram-negative Klebsiella', penicillin will be of no value, nor will erythromycin be effective. However, this organism is susceptible to tetracycline. If the pathogen should turn out to be gram-positive Streptococcus or Staphylococcus, then penicillin, erythromycin, and tetracycline may all be effective against it.

Penicillin, however, in addition to having a limited spectrum, also causes many minor and some serious sensitivity reactions. In a recent survey it was found that penicillin produced severe skin reactions. But most important was the observation that anaphylactic shock, with a

fatality rate of about 9 per cent, was the most frequent serious reaction. Such severe reactions are almost always associated with parenteral administration.

The tetracyclines (e.g., TETREX) have the advantages of a broad range of antimicrobial activity and low toxicity. And in addition, the physician does not have to trouble himself or his patients with repeated blood studies when he prescribes TETREX. Minor reactions such as gastric upsets or mild skin rashes occur occasionally. The most serious side effects are staphylococcal and monilial overgrowth, but these are rare and can be adequately controlled.

Some Microorganisms Susceptible^a to Tetracycline (TETREX)^b

Streptococcus; Staphylococcus; Pneumococcus; Gonococcus; Meningococcus; C. diphtheriae; B. anthracis; E. coli; Proteus; A. aerogenes; K. pneumoniae; Shigella; Brucella; P. tularensis; H. influenzae; T. pallidum; Rickettsiae; Viruses of psittacosis and ornithosis, lymphogranuloma inguinale, primary atypical pneumonia; E. histolytica; D. granulomatosis.

a Some strains are not susceptible.

^bTable adapted from Goodman, L. S., and Gilman, A.: The Pharmaceutical Basis of Therapeutics, 2nd edition, New York, The Macmillan Co., 1956, pp. 1322-1323

High blood, body fluid, and tissue levels of active drug are quickly attained when the new phosphate preparation of tetracycline (TETREX) is used.

The semisynthetic tetracyclines have been in constant use since they were introduced in 1952. They have been proved clinically and have established themselves as safe, effective, and valuable antibiotic agents. But the final decision, the choice of agent, and the control of therapy must remain where it has always been, in the hands of the individual physician.

References: 1. Zinsser, H.: A Textbook of Bacteriology. 11th edition, New York, Appleton-Century-Crofts, 1957, p. 409, 2. Welch, H.: Lewis, C. H.; Weinstein, H. I., and Boeckman, B. B.: Severe reactions to antibiotics. A nationwide survey. Antibiotic Med. & Clin. Ther. 4:800 (December) 1957.

BRISTOL LABORATORIES
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Of course, women like "Premarin"

THERAPY for the menopause syndrome should relieve not only the psychic instability attendant the ondition, but the vasomotor instability of estrogen ecline as well. Though they would have a hard time xplaining it in such medical terms, this is the reason romen like "Premarin."

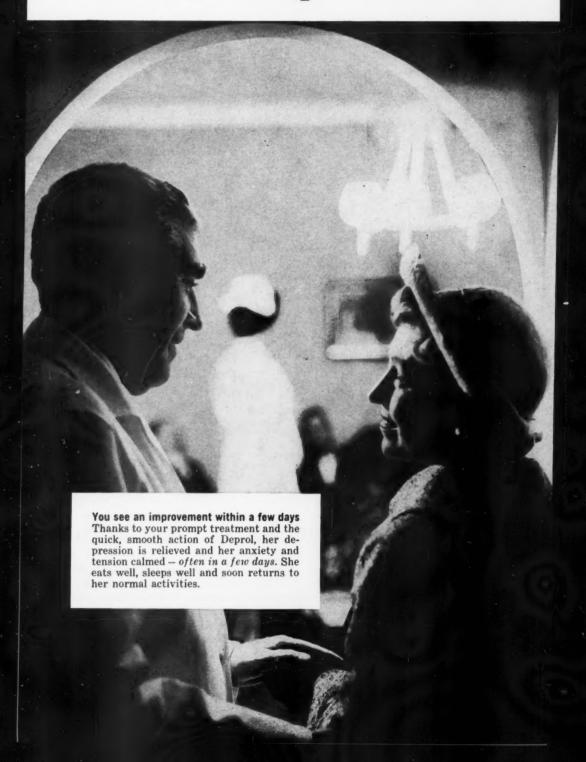
The patient isn't alone in her devotion to this natural strogen. Doctors, husbands, and family all like what does for the patient, the wife, and the homemaker. When, because of the menopause, the psyche needs

nursing — "Premarin" nurses. When hot flushes need suppressing, "Premarin" suppresses. In short, when you want to treat the whole menopause, (and how else is it to be treated?), let your choice be "Premarin," a complete natural estrogen complex.

"Premarin," conjugated estrogens (equine), is available as tablets and liquid, and also in combination with meprobamate or methyltestosterone.

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Lifts depression..



as it calms anxiety!

Smooth, balanced action lifts depression as it calms anxiety... swiftly and safely

Balances the mood - no "seesaw" effect of amphetamine-barbiturates and energizers. While amphetamines and energizers may stimulate the patient - they often aggravate anxiety and tension. And although amphetamine-barbiturate combinations may counteract excessive stimulation - they often deepen depression.

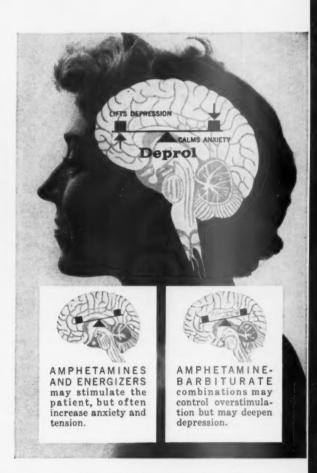
In contrast to such "seesaw" effects, Deprol lifts depression as it calms anxiety - both at the same time.

Acts swiftly — the patient often feels better within a few days. Unlike the delayed action of other drugs which may take two to six weeks to bring results, Deprol's smooth, immediate action relieves the patient quickly—often within a few days.

Acts safely - no risk of liver damage. Deprol does not produce liver damage, hypotension, psychotic reactions or changes in sexual function-frequently reported with other drugs.

BIBLIOGRAPHY (10 clinical studies, 714 patients):

1. Alsonder, L. (135 patients): Chemotherapy of depression — Use of megrobomate combined with beneficipine (2-diathylominosthyl benzilaria) hydrochloride. J.A.M.A. 100 (101, March 1, 1926. 2. Boteman, J. C. and Disconding and Company of the Company of the



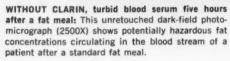
Dusage: Usual starting dose is 1 tablet q.i.d. When necessary, this dose may be gradually increased up to 3 tablets q.i.d. Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate. Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.





Clarin* can do this for your postcoronary patients





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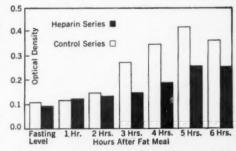
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- 1. Fuller, H. L.: Angiology 9:311 (Oct.) 1958.
- 2. Shaftel, H. E., and Selman, D.: Angiology 10:131 (June)



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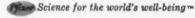
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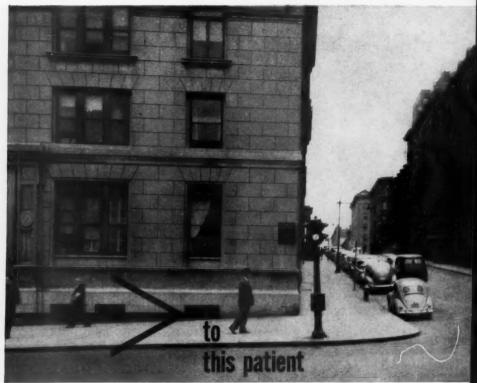
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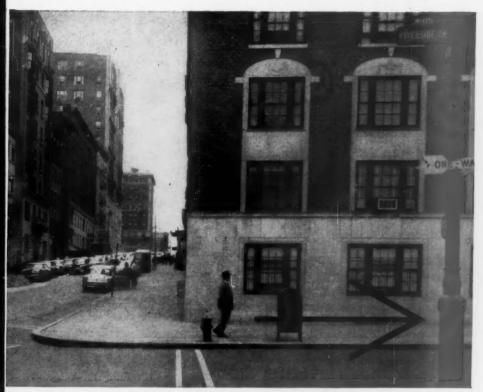
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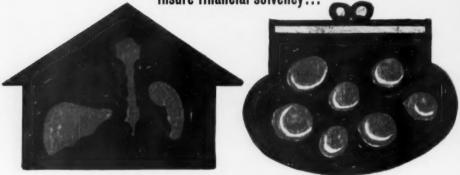
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(1) Holly, R. G.: Postgrad. Med. 26:418, 1959. (2) Evans, L. A. J., in Wallerstein, R. O., and Mettier, S. R.; Iron in Clinical Medicine, Berkeley, Univ. California Press, 1958, p. 170. (3) Schwartz, L.; Greenwald, J. C., and Tendler, D.: Am. J. Obst. & Gynec. 75:829, 1958.

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THE AMERICAN COLLEGE OF PHYSICIANS Schedule of Postgraduate Courses, Spring, 1960

| | March | | April | _ | | May | | | June | e |
|--|---------------------|-----------|-------|-------|-----|------|-------|---------------|------|------------|
| The following courses have been arranged through the generous cooperation of the directors and the institutions at which the courses will be given. Customary tuition fees will be: members, \$80.00. Full details of these courses may be obtained through the Executive Offices of the College, 4200 Pine St., Philadelphia 4, Pa. | 21-25 1 lingA-82 | 8-4 | 51-11 | 72-22 | 5-6 | 6-13 | 73-27 | May 30-June 3 | 01-9 | 13-17 |
| Course No. 1, RECENT ADVANCES IN PHARMACOTHERAPY: University of Washington School of Medicine, Seattle, Wash.; Robert H. Williams, M.D., F.A.C.P., Director. | × | .3i1 | 1 | | 1 | | | | | |
| Course No. 2, CURRENT CONCEPTS IN GASTROENTEROLOGY: Tulane and Louisiana State Universities Schools of Medicine, New Orleans, La.; G. Gordon McHardy, M.D., F.A.C.P., Director; Robert L. Simmons, M.D., and Helen Von Fossen, M.D., Associate Directors. | 18-82 | cisco, Ca | | | | | 1 | | | Fla. |
| Course No. 3, DERMATOLOGY FOR THE INTERNIST: University of Michigan Medical School, Ann Arbor, Mich.; Arthur C. Curtis, M.D., F.A.C.P., Director; E. Richard Harrell, M.D., Co-director. | | Fran | | × | 1 | | | | | ,imsil |
| Course No. 4, THE EARLY DETECTION AND PREVENTION OF DISEASES: University of Pennsylvania School of Medicine, Department of Public Health and Preventive Medicine, Philadelphia, Pa.: John P. Hubbard, M.D., F.A.C.P., and Norbert J. Roberts, M.D., F.A.C.P., Co-directors. | | is , nois | | 1 | 1 | × | 1 | | | A , gnites |
| Course No. 5, CURRENT RESEARCH IN CARDIOVASCULAR DISEASES: National Heart Institute, Bethesda, Md.; Luther L. Terry, M.D., F.A.C.P., Director. | | saS lau | | 1 | 1 | × | | | | M .A. |
| COUTSE NO. 6, THE HYPERTENSIVE DISEASES: DIAGNOSTIC AND THERAPEUTIC PROCEDURES IN ESSENTIAL, ADRENAL AND RENAL HYPERTENSION: Boston University School of Medicine, Massachusetts Memorial Hospitals, Boston, Mass.; Robert W. Wilkins, M.D., F.A.C.P., Director. | | nnA .4. | | | | | 23-26 | | | M.A |
| Course No. 7, INTERNAL MEDICINE: Indiana University School of Medicine, Indianapolis, Ind.; John B. Hickam, M.D., F.A.C.P., Director. | |).A | | 1 | | | | | | × |

The following courses are scheduled for FALL, 1960: HEMATOLOGY and RADIOISOTOPES, Ohio State Univ. College of Med., Sept. 19-23; CANCER AND THE INTERNIST, Memorial Sloan-Kettering Cancer Center, New York, Oct. 10-14; ELECTROCARDIOGRAPHY, Univ. of Utah, Nov. 14-19; GROWTH AND AGING, Lankenau Hosp. (tentative, Jan., 1961); INTERNAL MEDICINE, Univ. of Texas—Medical Branch, Galveston.





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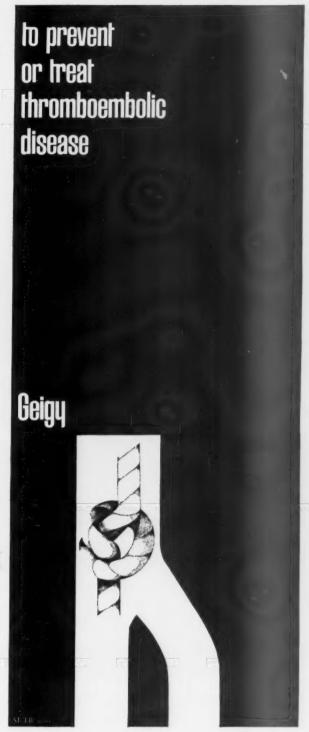
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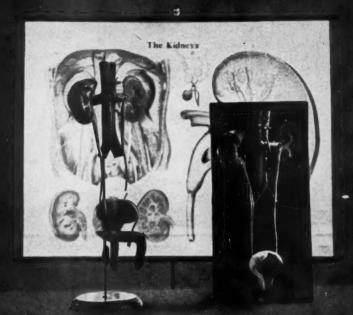
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OVER-ALL RESPONSE OF GRAM-HEGATIVE BACTERIA TO ANTIMICROBIAL DRUGS?

| | No. organisms tested | No. | sensitive (%) | | No. moderately resistant (%) | | resistant (%) |
|-----------------|-------------------------|-------------|------------------|-----|------------------------------|------|------------------|
| Nitrofurantoin | 1730 | 1074 | (62.1%) | | - | 656 | (37.9%) |
| Tetracycline | 2879 | 1000 | (34.7%) | 434 | (15.1%) | 1445 | (50.2%) |
| Chloramphenicol | 2879 | 1268 | (44.0%) | 725 | (25.2%) | 886 | (30.8%) |
| Streptomycin | 2879 | 943 (32.8%) | | 368 | (12.8%) | 1568 | (54.4%) |
| Sulfisoxazole | 1730 | 452 | (26.1%) | | - | | (73.9%) |

"In order of decreasing effectiveness, the activity of the drugs against gram-negative organisms was as follows: nitrofurantoin, chloramphenicol, tetracycline, streptomycin, and sulfisoxazole."

OVER-ALL RESPONSE OF GRAM-POSITIVE BACTERIA TO ANTIMICROBIAL DRUGS?

| | No. organisms tested | No. | sensitive (%) | | noderately stant (%) | | resistant |
|-----------------|-------------------------|------|---------------|-----|-------------------------|------|-----------|
| Nitrofurantoin | 320 | 289 | (90.3%) | | - | 31 | (9.7%) |
| Penicillin | 2353 | 515 | (21.9%) | 303 | (12.9%) | 1535 | (65.2%) |
| Erythromycin | 2353 | 1633 | (69.4%) | 308 | (13.1%) | 412 | (17.5%) |
| Tetracycline | 2353 | 987 | (41.9%) | 673 | (28.6%) | 693 | (29.5%) |
| Chloramphenicol | 1939 | 1593 | (82.2%) | 242 | (12.5%) | 104 | (5.3%) |
| Sulfisoxazole | 303 | 25 | (8.3%) | | - | 278 | (91.7%) |

"For the gram-positive organisms, the order of decreasing effectiveness was: nitrofurantoin, chloramphenicol, erythromycin, tetracycline, penicillin, and sulfisoxazole, although relatively few strains were tested against the first and last drugs."

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References: 1. Seneca, H., and Lattimer, J. K.: A.M.A. Arch. Path. 64:481, 1957. 2. Waisbren, B. A., and Crowley, W.: A.M.A. Arch. Int. M. 95:653, 1955. 3. Metzger, W. I.: Antibiotics Annual 1958-1959, edited by H. Welch and F. Marti-Ibanez, New York, Medical Encyclopedia, Inc., 1959, pp. 966-971.

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| Nasal congestion | 7 | 7 | 0 |
| Gastrointestinal disturbances | 2 | 0 | 2 |
| Conjunctivitis | 1 | 1 | 0 |

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- 1. Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. 169:1609 (April 4) 1959.
- 2. Bartels, C. C.: N. E. J. Med. 261:785 (Oct. 15) 1959.

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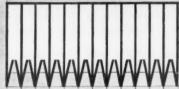
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Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958. 2. Bunim, J. J., et al.: Paper read before the Am. Rheum. Assoc.,

2. Bulling, 1.5., et al.: Faper Leab device the Mil. Antesin. Associ.
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ANNALS OF INTERNAL MEDICINE

VOLUME 52

MARCH, 1960

NUMBER 3

RESULTS OF 1,000 CONSECUTIVE BASAL GANGLIA OPERATIONS FOR PARKINSONISM * †

By IRVING S. COOPER, M.D., New York, N. Y.

During the last seven and one-half years my associates and I have had the opportunity of examining in considerable detail 5,000 patients with parkinsonism. Of these, 1,000 were submitted to surgery of the basal ganglia in the form of anterior choroidal artery occlusion, or chemopallidectomy or chemothalamectomy. It is the purpose of this report to summarize briefly the pertinent clinical data of this investigation.

Although the primary aim of our investigation has been the development of an accurate, relatively certain, practical and safe means of relieving the tremor and rigidity of parkinsonism by basal ganglia surgery, a multidisciplinary investigation has been carried out to give each patient the advantage of focusing the attention of several specialties on each case, as well as to enable us to gather as much information as possible about parkinsonism and its pathophysiologic basis.

It must be stated at the outset that it would be impossible to present in this brief paper all of the detailed data, documentation and findings upon which this report is based. Rather, this paper will summarize certain clinical and surgical highlights which we believe are worthy of immediate attention. For a more meticulous resumé of individual case reports, operative technic, roentgenologic findings and diverse physiologic observations, reference to previous reports 1, 2, 3, 4 and to a fully documented monograph 5 now in press will be necessary.

* Received for publication July 27, 1959.
From the Department of Neurosurgery, St. Barnabas Hospital, and the Division of

Neuromuscular Disorders, New York University Post-Graduate School of Medicine.
†Assisted by grants from Sister Elizabeth Kenny Foundation, The Allan P. and Josephine B. Green Foundation and the Office of Vocational Rehabilitation of the Department of Health, Education, and Welfare.

Requests for reprints should be addressed to Irving S. Cooper, M.D., Director, Department of Neurologic Surgery, St. Barnabas Hospital for Chronic Diseases, Third Avenue, New York 57, N. Y.

VARIOUS ASPECTS OF THE PROBLEM

During the early stages of our surgical investigation our problem was to determine whether the tremor and rigidity of parkinsonism could be completely relieved without inducing any neurologic or psychologic deficit in the patient. That this could be done routinely became apparent in the early stages of our investigation, and that such complete relief of tremor and rigidity is lasting has been proved by documented follow-up studies which, in some of the earlier cases, have now passed their sixth year.

The second aspect of our problem was to modify our original basal ganglia operation so as to make it relatively certain in its effects, safe, accurate, and capable of reproduction in many clinics. With the use of chemothalamectomy as currently employed on our service, such a procedure has been developed. In carefully selected candidates, disabling tremor and rigidity can be relieved by chemothalamectomy in more than 85% of cases,

with a risk of mortality of 2%.

The third aspect of our problem, and an exceedingly important and often overlooked one, has been to arrive at a better understanding of the multifaceted syndrome of parkinsonism itself. To this end, the intensive efforts of many specialties have been concentrated on the large amount of clinical material we have seen on our service. Each patient has been evaluated preoperatively and postoperatively not only by the neurosurgical team but also by an internist, a clinical psychologist, a medical neurologist, a physiatrist, a speech therapist and, in most instances, by at least one disinterested observer from some clinic other than our own. Although these evaluations were originally instituted to serve as severe tests of the effects of surgical intervention in parkinsonism, it has become apparent that considerable data exist which contribute to an understanding of the basic problem itself, namely, the problem of parkinsonism and its effect upon the patient.

THE MANY SYNDROMES OF PARKINSONISM

Parkinsonism is a far more complicated, variable and protean syndrome than has been indicated in most publications up to the present time. The excellent descriptive qualities of Parkinson's original report upon the shaking palsy have caused many to lose sight of the fact that this report was based upon the meticulous observation of only six cases. A more far-reaching,

physiologic classification of the syndrome is now necessary.

The extreme variability of progress of the disease in individual cases is one striking feature. Some patients become completely incapacitated by bilateral parkinsonism within two years of onset, while others suffer only from tremor and rigidity of the extremities of one side of the body for as long as 25 years after onset of the disease. Although each may be considered to have parkinsonism, it is evident that the latter represents a benign form of the syndrome, whereas the former may manifest deformities, vegetative phenomena, dysphonia, dysphagia, and often psychologic changes in

addition to the incapacitating bilateral tremor and rigidity. To deal with each case rationally, it is necessary to supplement each diagnosis of parkinsonism by a brief, pertinent description of the various aspects of the total syndrome a particular patient demonstrates.

Although the triad of tremor, rigidity and abnormal gait has become virtually synonymous with the syndrome of parkinsonism, there are other manifestations which may assume major importance in certain cases. Bradykinesia—extreme slowness of movement—is a common symptom. It must be clearly demonstrated whether the bradykinesia is secondary to rigidity. If it is related to rigidity, the patient under some circumstances will demonstrate the ability to move rapidly. However, there is also a type of bradykinesia, recently described by Schwab ⁶ as the akinetic variety of parkinsonism, in which the primary disabling symptoms are muscular weakness and poverty of movement, without the presence of objective rigidity. This distinction is important, because the type of patient who demonstrates bradykinesia secondary to rigidity is an excellent candidate for neurosurgical treatment, whereas such treatment may be contraindicated in the patient with the nonrigid, akinetic variety of parkinsonism.

Masked facies, oculogyric crisis, spontaneous crying or laughing, respiratory difficulties in the form of uncontrollable overbreathing, as well as vegetative phenomena such as spontaneous hyperthermia and excessive sweating, are common manifestations. Dysphagia and dysphonia are almost invariably present in the advanced case. All of these signs must be evaluated carefully in delineating the type of parkinsonism a particular patient has, and in studying any potential candidate for surgical treatment.

One other area of symptomatology often observed in patients with parkinsonism—namely, psychologic and emotional disturbances—has not received sufficient attention. Although Parkinson stated that the intellect is not impaired by shaking palsy, he neglected to emphasize the frequent incidence of psychologic abnormalities in such cases. Actually, in many instances psychiatric disturbances play an important role in the course of this illness.

Organic mental symptoms may be seen in patients with parkinsonism, particularly in those in the older age groups. In some instances, patients with presentle or senile dementia demonstrate a senile type of resting tremor. Such cases should not be classified as parkinsonism, but rather as senile brain disease with organic mental deterioration and tremor. Obviously, as far as prognosis and therapy are concerned, this distinction is important, and it has been neglected to a surprising degree.

Latent schizophrenia, anxiety, panic states, pathologic passivity and dependency, rigid personality, psychotic depression and extreme over-reaction to stress are common manifestations in this group of patients. These must be evaluated with interest and understanding in each case before any meaningful type of therapy can be planned.

We have been particularly impressed with the large percentage of patients who insist that neither tremor nor rigidity was present until they were subjected to a particularly stressful situation of either an emotional or a physical nature. Moreover during the course of the illness, similar stress is often followed by marked exacerbation of all parkinsonian symptoms which may last for months or which may accelerate the progress of the disease.

In some instances a parkinsonian patient who has been ambulatory and self-sufficient in his activities of daily living may become bed-ridden and virtually immobile following an incident which would ordinarily provoke only a mild anxiety in a nonparkinsonian individual. In such cases the patient often becomes hyperpyretic and incontinent, and sometimes mentally confused or actually psychotic. Such a reaction to stress is usually observed in the rapidly progressive, malignant form of the disease referred to earlier.

It is important to evaluate each patient's reaction to stress when determining the prognosis and treatment of choice of an individual case. The exacerbation of symptoms of a motor, mental and vegetative variety produced by psychologic or emotional stress, physical trauma or, in some instances, an operation, should be considered as an exaggeration of the existing syndrome, or a hyperparkinsonian crisis.

MEDICAL THERAPY

At the present time there is no medicinal agent which can cure any single component of the parkinsonian syndrome, or halt the progress of the disease, or reverse the tremor, rigidity or deformity associated with parkinsonism. Generally, one can expect a 15 to 25% functional improvement of a transitory nature in about 60 to 80% of cases where drug therapy is intelligently applied. An excellent summary of current drug therapy for Parkinson's disease, recently presented by Schwab and England, deserves widespread attention. In addition to drug therapy, which should be given a trial in each case of parkinsonism, the physician must supply a high degree of compassionate interest, and should consider, as adjunctive therapies, psychotherapy, physiotherapy and speech therapy. All of these measures, however, are at best temporizing, for none will halt the inexorable progress of the disease which, in the large majority of cases, unless reversed, will lead to incapacitation and helplessness.

CHEMOPALLIDECTOMY AND THALAMECTOMY

Surgery of the basal ganglia, if properly performed on patients who have been meticulously selected, is capable of producing complete relief of tremor and rigidity of the extremities contralateral to operation in more than 85% of cases, with a risk of mortality in 2%, and a risk of hemiparesis or other neurologic complication in 3%. Because this type of surgery has been de-

veloped relatively recently, there are as yet few clinics which have reproduced these statistics in a large series of cases. However, in several centers similar results have been achieved, and these are increasing in number as experience is gained in this relatively new field of brain surgery.

I should like to review the steplike progression that has led, during our

investigations, to our present statistics and conclusions.

In 1953, in reporting the fact that anterior choroidal artery occlusion had successfully relieved tremor and rigidity of parkinsonism without inflicting any neurologic deficit in selected cases. I reported that our findings were of interest physiologically and deserving of further study clinically. No mention was made at that time of actual therapeutic application. In 1954, following further encouraging experience with this technic, it was pointed out that far advanced tremor, rigidity and incapacitation had been relieved, and that such relief had lasted at that time for more than one year. It was concluded that investigative use of this procedure would be warranted, but only in far advanced, incapacitated cases.² In 1953, early experiments with chemopallidectomy were reported.3 In 1955 we reported that further experience with anterior choroidal artery occlusion and chemopallidectomy had produced relief of tremor and rigidity which had endured, and for the first time stated that cautious optimism was warranted regarding the future application of surgical therapy to the previously intractable disease of parkinsonism.4 However, we still advised that the procedure be used principally in far advanced, incapacitated patients, and that it not be employed until the patient was virtually helpless.

By 1956 we were able to report that, without question, the tremor and rigidity of parkinsonism could be relieved neurosurgically without sacrificing motor, sensory or intellectual faculties, that the relief of symptoms had endured up to that time for three years, that the risk of operation had been reduced to between 3 and 4%, and that 70% of cases who were carefully selected would obtain satisfactory, lasting results. Our experience at that time was based on 145 cases. It is only within the last three years, as our experience has grown to more than 1,000 operations, and as we have become better informed regarding the manifold symptomatology of parkinsonism, and have perfected our operative technic by a series of modifications, that we have been able to increase the percentage of successful results to more than 85%, to reduce the risk of mortality to 2%, and to state with certainty that six-year cures of tremor, rigidity and incapacitation are now demonstrable. ^{10, 11}

On the basis of this experience, and the secure knowledge that it can be reproduced in competent hands, it is concluded that surgery for progressive tremor, rigidity and incapacitation is indicated in a large number of parkinsonian patients, that it should be performed relatively early in the course of the disease, before the patient becomes incapacitated, and that it is the treatment of choice in many instances.

THE BASIC PREMISE OF CHEMOPALLIDECTOMY AND THALAMECTOMY: A CLINICOPHYSIOLOGIC OPERATION

The single most important component of chemothalamectomy or pallidectomy is the necessity of producing a reversible, harmless lesion within the target area of the brain, the effects of which can be evaluated in a conscious, coöperative patient, before any permanent lesion is inflicted in the brain of this particular patient.

This clinicophysiologic surgical test of the planned lesion is the absolute foundation upon which safe, successful basal ganglia surgery is based.

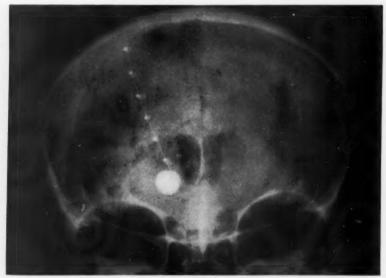


Fig. 1. Roentgenogram demonstrating balloon cannula in place in the thalamus, with distention of the balloon within the thalamus by 0.5 c.c. of Hypaque. Distention of this balloon in the basal ganglia provides a clinical-physiologic test. When the balloon is distended in the proper locus in a conscious, coöperative patient, tremor and rigidity are immediately relieved in the contralateral extremities.

Because of the anatomic, physiologic and pathologic variations in the brains of human beings with parkinsonism, the selection of a fixed small area of the brain for destruction in each patient presenting a diagnosis of parkinsonism is not practicable or desirable. Percival Bailey, who has compiled the most detailed stereotactic atlas of the human brain thus far achieved, concluded his years of study of this problem by stating that anatomic localization alone is insufficient to permit a lesion to be placed safely deep within the brain, and that physiologic confirmation is required.¹² Since the inception of chemopallidectomy and thalamectomy, we have insisted upon the fact that one must first evaluate the effects of a particular lesion in a par-

ticular site within the brain of each patient before one is justified in inflicting a permanent lesion. Within the last few years, virtually every investigator working within this field of the production of deep brain lesions in humans has reached the same conclusion.

The physiologic test which we carry out at the present time in each patient with parkinsonism, is the introduction, simply and quickly, through a trephine opening the size of a ten-cent piece, of a brain cannula into the region of the lateral ventral nucleus of the thalamus, or whichever other target area we wish to approach. When this has been accomplished, a small balloon at the tip of the cannula is distended with 0.5 c.c. of Hypaque. This balloon produces a compressive effect upon the structures in this region of the brain and, when it has been properly placed, immediately results in ces-

sation of contralateral tremor and rigidity (figure 1).

When one has achieved the desired effect, and examines the conscious, cooperative patient to ascertain that no undesirable motor, sensory or psychic effects will be induced by this particular lesion, one can proceed with completion of the permanent lesion by injection of the neurolytic agent into the proved site. The infliction of a permanent lesion within the basal ganglia of the brain of humans without the performance of a reversible test is unjustified. If one chooses to perform this type of surgery under deep general anesthesia,13 the incidence of successful results will be less and the incidence of undesirable complications will be greater. If one chooses to perform this type of surgery based solely upon anatomic landmarks, no matter how accurate the surgical instrumentation may be, the degree of successful intervention will be less and the degree of complications will be greater.

Roentgeno-anatomic localization, plus clinicophysiologic confirmation of correct and sufficiently large lesion placement, must be utilized to achieve consistent relief of tremor and rigidity combined with a high degree of safety.

CHEMOPALLIDECTOMY AND THALAMECTOMY

The production of a sufficiently large lesion in the globus pallidus by the technic of chemopallidectomy proved to be a relatively simple procedure, and favorable results were obtained in 70% of the cases. However, although rigidity could be relieved in 80% of such cases, tremor was relieved in only 60%. In such instances the tremor would respond favorably when we placed a second lesion within the lateral portion of the thalamus.

In subsequent experience with several hundred cases, this latter lesion in the region of the ventrolateral nucleus of the thalamus proved to be so successful for cases that had been incompletely relieved of tremor by the pallidal lesion alone that it gradually became our practice to produce a thalamic lesion as the lesion of choice. We have learned that when this thalamic lesion is properly placed, virtually complete relief of tremor and rigidity is obtained in 90% of cases of properly selected patients. Moreover, this relief is complete and lasting. There is no question but that a

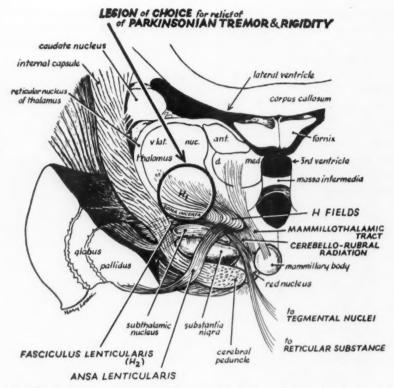


Fig. 2. Anatomic representation of the lesion of choice in the lateral ventral nucleus of the thalamus. Note that this lesion involves the reticular nucleus, the zona incerta, and terminations of the fascicular and ansa lenticularis, as well as the termination of pathways arriving from the red nucleus and cerebellum.

lesion in the region of the ventrolateral nucleus of the thalamus—which, of course, encompasses many nearby neurologic pathways and structures, as indicated in figure 2—has a more certain, complete and absolute effect on contralateral resting tremor than does the pallidal lesion. This thalamic lesion is now the lesion of choice for neurosurgical relief of tremor and rigidity.

RESULTS

In the analysis of this entire series of 1,000 consecutive operations, if one includes all three procedures which have been performed—anterior choroidal artery occlusion, chemopallidectomy and chemothalamectomy—and further includes the statistics on every case since the first experimental occlusion of the anterior choroidal artery, it can be stated that lasting relief of tremor and rigidity has been achieved in 75% of cases in the extremities contra-

lateral to the side of operation. On the other hand, in an evaluation of the last 500 cases of chemothalamectomy (without question the procedure of choice), it can be stated that more than 85% of the cases selected for surgery have demonstrated virtually complete relief of contralateral tremor and rigidity which has endured up to the time of this report. One may break this down still further by stating that, in the ideal candidate—that is, a case where tremor and rigidity exist predominantly in the extremities of one side and the patient has not yet become incapacitated—there is a 90% chance on our service of obtaining relief of tremor and rigidity by chemothalamectomy.

These operations have as a principal function and goal the relief of resting tremor and rigidity, and the attendant bradykinesia, gait abnormalities and general motor dysfunctions. By and large, weakness and monotony of the spoken voice, difficulty in swallowing, and excessive salivation have not been benefited by operation. On the other hand, in about one-half of the cases with these symptoms, oculogyric crisis and profuse perspiration have

been ameliorated following surgery.

It should be emphasized that the relief of tremor, rigidity, deformity and bradykinesia obtained by chemothalamectomy results in a marked degree of functional improvement in all activities of daily living. Generally, the degree of improvement obtained and the degree of normality which can be regained by the patient depend upon the extent to which the disease has ravaged the patient prior to surgery. If the patient has only unilateral involvement—that is, tremor and rigidity of the extremities of one side of the body—he can be returned to a state of normality approximating his condition before the onset of parkinsonism. The following examples may be cited:

CASE REPORTS

Case 1. A 39 year old white male had had parkinsonism for 12 years and had not worked for seven years because of marked tremor, rigidity and deformity of the right extremities. Chemopallidectomy, performed in February, 1955, resulted in 100% relief of tremor, rigidity and deformity of the right extremities. This relief has lasted up to the present time, and the patient is employed full-time as an assistant physiotherapist at one of the United Mine Worker hospitals in Kentucky. He has absolutely no sign or symptom of parkinsonism.

Case 2. A 58 year old white male was unable to work for three years prior to operation because of severe tremor and rigidity of the right extremities. He had previously earned his living as a professional magician. Chemothalamectomy was performed in November, 1957. Complete relief of tremor and rigidity was obtained, and the patient was restored to a condition of normality. He has since been able to return to his activities as a magician, and his previously incapacitated right hand is

now normal and once again faster than the eye.

Case 3. A 50 year old minister was obliged to give up his calling and relinquish his responsibilities in his parish because of severe, progressive tremor and rigidity of the right extremities of four years' duration. Chemothalamectomy, performed in October, 1957, resulted in complete relief of all tremor and rigidity of the right

extremities, and the patient has since appeared to be completely normal. He states that there is no way to tell that he ever had parkinsonism. He has been able to return to full-time duties as a minister, and carries them out without difficulty.

Case 4. A 70 year old business executive had become incapacitated for work and for his activities of daily living by progressive tremor and rigidity of the left extremities of seven years' duration. Chemopallidothalamectomy, performed in November, 1957, has resulted in complete relief of tremor and rigidity of the left extremities. Not only has the patient been able to return to his duties as chairman of the board of a large corporation, but he has also been completely self-sufficient in all activities of daily living, and has actually returned to piloting his own airplane.

The above cases demonstrate the type of result that can be obtained in ideal unilateral candidates for surgery. In our hands, complete relief of tremor and rigidity can be produced by chemothalamectomy in nine out of 10 of such cases, restoring these patients to a relatively normal condition.

If a patient has bilateral parkinsonism of an advanced degree, even though he may be bedridden in some instances, a surprising degree of functional improvement can often be obtained. In some instances, such a completely incapacitated patient can be restored to independence in all activities of daily living. Naturally, in this type of advanced problem, the criteria for selection of cases referred to earlier must be strictly adhered to. An example of such an incapacitated case restored to asymptomatic and functional well-being may be cited.

Case 5. A 46 year old white male had been helpless from bilateral postencephalitic parkinsonism since 1933. From 1948 until 1954 he was completely bedridden and totally incapacitated in every activity of daily living. In May, 1954, he underwent a left anterior choroidal artery occlusion which completely relieved tremor and rigidity of the right extremities. Within five days after operation he was ambulatory. One year later a right chemopallidectomy was performed which resulted in relief of left-sided tremor and rigidity. Since that time the patient has been free of tremor and rigidity on both sides of his body, has been independent in all activities of daily living, and has actually returned to gainful employment. This patient, although free of tremor and rigidity and independent functionally, still retains certain stigmata of parkinsonism, such as impoverished speech and excessive salivation.

In our series of cases, as well as in parallel series of other investigators, one finds that the results are directly proportionate not only to the proper performance of the operative procedure but also to the type of patient operated upon. Thus, one must be as meticulous in the selection of candidates for surgical intervention as in the performance of the surgery and the postoperative care of the patient.

INDICATIONS FOR OPERATION

The primary indications for basal ganglia surgery in parkinsonism are tremor and rigidity, either alone or in combination. It is these symptoms and their attendant disabilities, such as bradykinesia, muscular cramps, impaired motor function, masked facies and poor gait, which basal ganglia

surgery has successfully relieved. Therefore, these should be the primary symptoms in any case being considered for surgical therapy. Even though other manifestations of the parkinsonian syndrome may exist, the physician and the patient should understand that it is primarily the symptoms enumerated above that successful basal ganglia surgery is capable of alleviating.

The ideal surgical candidate is a patient who has not demonstrated any intellectual or psychologic abnormalities, and who has relatively few symptoms except for tremor or rigidity, or both, and the disabilities which these symptoms produce. Further, it is advisable that surgery be seriously considered before the disease becomes frankly bilateral, although the majority of cases operated upon in our series thus far had already become bilateral prior to surgery. Nevertheless, it should be pointed out that a patient with unilateral tremor and rigidity has a 90% chance of obtaining relief of these symptoms and of being discharged from the hospital approximately eight to 10 days after surgery. As the disease progresses, and generalized incapacitation becomes more advanced, and as other symptoms of parkinsonism become more marked, the postoperative course is necessarily prolonged, and the statistical chance of complete alleviation of symptoms is reduced to 80%.

Surgery should often be electively performed while tremor and rigidity are isolated to the extremities of one side in cases where these symptoms interfere with ability to work or to perform daily activities. Moreover, it is mandatory that surgical therapy be given painstaking consideration as soon as there is evidence that these symptoms are becoming bilateral, inasmuch as, once the disease makes its appearance bilaterally, progressive incapacitation of a serious nature is inevitable. As a rule of thumb, I would advise that any male patient have an opportunity to be evaluated for surgical therapy when his ability to earn a livelihood becomes threatened by his symptoms of tremor and rigidity. For the female patient, as soon as her ability to attend to the needs of her children and of the household becomes seriously handicapped, surgery will probably be indicated.

In our experience, chronologic age has no specific bearing upon the result obtained from surgery. We have found that patients in the seventh and eighth decades of life are capable of withstanding this surgery almost as well as much younger patients, and have achieved results which are comparable. However, it is mandatory that patients over the age of 65 be operated upon at an earlier stage of the disease than patients in the fourth and fifth decades of life. One may operate upon a relatively young individual who has far advanced bilateral parkinsonism and is already chairridden or even bedridden. If tremor and rigidity are relieved in such a patient, he is able to resume activities which had been impossible for many years. On the other hand, if one operates upon a similar patient who is 70 years of age, even though tremor and rigidity may be relieved, rehabilitation is infinitely more difficult and often less rewarding. Thus, one may operate

upon an aged patient who is in good mental and physical condition and anticipate an excellent result if the disease is only moderately advanced. However, the combination of advanced age and bilateral incapacitating disease often makes surgical intervention unwise.

In each case the patient and his physician must weigh the risks involved in the prolonged medical therapy of parkinsonism against the risks involved in surgery. In the patient who is not operated upon there is an almost certain risk of gradual, creeping incapacitation and helplessness, which will endure for the lifetime of the patient and often render him motionless and shaking, unable to communicate with his environment, and deprived of the sensory stimulation essential to mental and physical well-being. Further, it often deprives the individual of his wage-earning and self-care abilities, and further incapacitates the one or more members of his family obliged to care for him. On the other hand, one must point out that this course does not ordinarily involve any risk of death from the disease itself.

The risks of the disease outlined above must be weighed against the risks of the operation. On our service, chemothalamectomy now carries a risk of mortality of 2%, and a risk of hemiparesis or other neurologic deficit of 3%. By and large, these are the only serious risks involved in this procedure. However, they are spelled out and underlined to each patient who considers undergoing the procedure. For patients with far advanced, bilateral parkinsonism who are helpless, there is the risk of postoperative morbidity—that is, prolonged hospitalization of three to six weeks. However, this is a transient phenomenon, and is usually well worth the patient's effort. In evaluation of these risks, the abovementioned benefits from this type of surgery must also be seriously considered. By balancing the relative risks of the disease against the relative risks of the operation, plus the possible gains of the operation, the physician may help each individual patient to reach a wise decision.

CONTRAINDICATIONS TO OPERATION

There are certain absolute contraindications to operation. First, one must carefully weed out all patients who have parkinsonism but do not have any significant degree of either tremor or rigidity. Usually, these patients will fall into the akinetic group described by Schwab, where there are primary motor weakness, bradykinesia, mental deterioration, and other evidences of central nervous system abnormality, but no significant degree of either tremor or rigidity. Obviously, such cases are not candidates for basal ganglia surgery.

Psychosis and organic mental deterioration are absolute contraindications to this type of surgery. Each of these symptoms may be aggravated by brain surgery. A systematic, detailed psychologic evaluation is mandatory in the preoperative evaluation of the patient with parkinsonism.

Advanced arteriosclerosis, heart disease and general medical abnormalities are to be considered relative contraindications. Autonomic symptoms accompanying parkinsonism, such as severe sweating, salivation, hyperpyrexia, urinary retention, and spontaneous laughing and crying, are relative contraindications, but must be evaluated in the context of the total clinical picture. In many instances, we have chosen to operate despite these particular symptoms. However, the postoperative course is usually prolonged in cases in whom such symptoms exist, and meticulous nursing care is required if the patients are to avoid postoperative pulmonary and metabolic difficulties.

Pseudobulbar palsy with inability to swallow usually contraindicates this type of surgery, since it is frequently indicative of brain stem involvement, and may be aggravated during the postoperative period.

Physiologic old age is a contraindication to surgery. A patient who may be 65 years of age but who appears to be much older, who is weak and feeble, and demonstrates early signs of senility, should not be operated upon, even though it appears that tremor and rigidity could be satisfactorily relieved by operation. On the other hand, a patient who is 70 or more but who is intellectually vigorous and does not show obvious evidence of advanced arteriosclerosis, and whose disease has not progressed to a completely incapacitating state, may be considered for surgery and will do as well as patients who are much younger chronologically.

If one evaluates the particular symptoms the patient feels are incapacitating him or interfering with his ability to enjoy life, and weighs these against the total clinical picture the patient presents, one may successfully visualize exactly what the patient would be like postoperatively if his tremor and rigidity are successfully relieved. By this maneuver, one can logically conclude whether surgery is indicated or contraindicated in any particular case.

COMPLICATIONS

The incidence of mortality in these 1,000 operations of chemopallidectomy and chemothalamectomy has been 2.4%.

The incidence of lasting hemiplegia, hemiparesis or monoparesis has been 3%. Transient motor or sensory signs, disappearing during the first three postoperative weeks, have been observed in 6% of cases.

Some degree of somnolence, mental confusion or obtunding has been observed during the first postoperative week in 8% of cases; it may last several weeks in aged patients. However, this has invariably been transient, and in almost every instance has been an exaggeration of abnormalities noted during the preoperative psychologic examination.

Transient speech disturbances, varying from dysphonia to slurring of speech to mutism or aphasia, have been observed in 10% of cases. They have been more common following operations on the dominant hemisphere,

but have not been limited to the dominant hemisphere operations. These disturbances have tended to clear within two to three weeks in practically every instance. They are more common in patients in whom bilateral operation is performed.

Excessive drowsiness, hyperpyrexia, hypokinesia, dysphagia, aspiration pneumonitis and urinary retention are seen postoperatively in the far advanced postencephalitic cases, but have responded to meticulous nursing care.

Transient hyperkinetic states, varying from slight, fleeting choreic movements of one hand to hemiballismus, have been seen 36 times. In three cases these were very severe, but all disappeared spontaneously. One case, however, lasted four months.

Except for such isolated surgical complications as deep hemorrhage or infarction, which account for our mortality rate of 2.4%, and hemiplegia or hemiparesis in 3% of cases the postoperative problems are chiefly transient and seem to be directly related to the preoperative condition of the patient. They can almost be predicted by the preoperative evaluation. Although they are trying, and in some instances difficult to deal with, they do not affect the long-range favorable effect of the operation on the patient or his symptoms.

SUMMARY AND CONCLUSIONS

1. Since 1952, more than 1,000 basal ganglia operations for the tremor and rigidity of parkinsonism have been carried out on our service. These operations were performed either by the author or by neurosurgical residents under his immediate supervision.

2. Of the cases subjected to chemopallidectomy or chemothalamectomy, 80% obtained relief of tremor, rigidity and deformity, and attendant symptoms such as bradykinesia and gait and postural abnormalities. The mortality rate for the first 1,000 consecutive operations was 2.4%. The incidence of hemiparesis or hemiplegia was slightly less than 3%.

3. The tremor, rigidity and deformity of parkinsonism can be completely relieved by this type of surgery. Many five-year cures of these symptoms are now demonstrable in the personal series of cases reported in this paper.

4. Clinical physiologic testing of a reversible lesion placed in the thalamus or other site within the basal ganglia is essential if one hopes to reproduce consistent relief of parkinsonian tremor and rigidity, and to maintain a low incidence of risk. This clinical physiologic testing must be combined with correct roentgeno-anatomic localization of lesion placement, and the lesion in each case must be tailored to fit the requirements of the particular patient, if consistently safe and rewarding results are to be obtained.

5. The site of the lesion of choice for relief of parkinsonian tremor and rigidity is the region of the ventrolateral nucleus of the thalamus. Such a lesion includes the reticular nucleus of the thalamus, the zona incerta, and afferent fibers to the thalamus from the globus pallidus, cerebellum, red

nucleus and vestibular nucleus, as well as the efferent fibers to the cerebral cortex.

6. The meticulous selection of candidates for surgery is as important as the meticulous performance of the operation. Patients in the seventh and eighth decades of life may be operated upon with the same possibility of benefit as may those in the younger group, as long as they are selected in accordance with the requisites described in this report. The incidence of good results achieved by surgery will be directly proportional to the judgment and insight exercised in the selection of surgical candidates.

7. Surgical treatment of parkinsonian tremor and rigidity is now indicated relatively early in the course of the disease. Male patients should be operated upon before it is necessary for them to give up gainful employment. Female patients should be operated upon before they become unable

to carry out their activities of daily living independently.

8. Surgical therapy is now applicable to a large percentage of the parkinsonian population. Although medical therapy deserves a complete and definitive trial in each case, surgical therapy has certain irrefutable advantages once the case has been demonstrated to be progressive, and threatens interference with the activities of daily living, and eventual incapacitation. Surgical therapy can provide rapid and often complete relief of tremor, rigidity and deformity, and the attendant motor symptoms of bradykinesia, poverty of movement, and other functions-often to a remarkable degree. Not only does surgical therapy abolish these symptoms or reverse the deformities present, but it has also now been demonstrated that such relief of hyperkinetic phenomena has endured following operation for as long as six years, which is the present time limit of this study. Fiveand six-year cures of tremor, rigidity and motor abnormalities without any evidence of recurrence are well documented. In many instances there has been amelioration of the secondary parkinsonian symptoms, such as masked facies, excessive sweating and oculogyric crisis. However, it is to be emphasized that surgery is indicated only when the primary symptoms of tremor and rigidity are paramount. Surgical therapy offers the only means not only of reversing the motor symptoms which are present, but also of halting the progression of the disease in the extremities which are alleviated of these symptoms.

SUMMARIO IN INTERLINGUA

Iste reporto presenta un evalutation de 1000 consecutive operationes de ganglion basal effectuate pro parkinsonismo inter octobre 1952 e april 1959. Le typo de operation empleate in iste 1000 consecutive casos esseva chimopallidectomia o chimothalamectomia.

Il ha essite necessari modificar certe conceptos relative al syndrome de parkinsonismo le qual se ha revelate como un multo plus complexe e multo plus variabile gruppo de symptomas que lo que es indicate in le majoritate del publicationes apparite ante le tempore presente. Es includite in le presente reporto un description del varie typos de parkinsonismo, variante ab casos con pur tremor o rigiditate usque a illos etiam manifestante un organic syndrome mental, paralyse pseudobulbar, phenomenos vegetative, e un symptomatologia psychotic. Es signalate que le operation del ganglion basal describite in le presente reporto visa al alleviamento de tremor e rigiditate e le concomitante invaliditates motori. Un comprension fundamental del multe syndromes includite sub le designation de parkinsonismo es essential pro le appropriate selection de candidatos pro un therapia chirurgic.

Ben que in nostre experientia le objectivo original del intervention chirurgic esseva le aspecto mesial del globo pallide, le evolution de iste typo de operation in nostre servicio ha demonstrate que le objectivo de election del intervention chirurgic pro le alleviamento de tremor e rigiditate parkinsonian es le nucleo ventrolateral del thalamo. Durante le passate duo annos, iste portion del thalamo esseva le exclusive area de lesiones producite pro le alleviamento de tremor e rigiditate. Le plus importante componente individual de chimothalamectomia es le necessitate de producer un reversibile e innocente lesion intra le area critic del cerebro—un lesion le effectos del qual pote esser evalutate in un conscie e plenmente cooperante patiente—ante que un lesion permanente es infligite al cerebro. Le uso de un micre inflationabile ballon al puncta de nostre cannula cerebral produce un effecto compressori super le nucleo ventrolateral del thalamo e servi assi a provider le test physiologic que es requirite in le conscie e cooperante patiente. Le lesion permanente es effectuate per le injection de un solution de Pantopaque in alcohol a in le cavitate producite per le supra-describite ballon.

Le experientia con nostre 1000 consecutive operationes demonstra conclusivemente que le tremor, le rigiditate, e le deformitate de parkinsonismo pote esser alleviate completemente per iste typo de intervention chirurgic. Numerose quintenne curas del mentionate symptomas es demonstrabile in le serie de casos personal que es reportate in le presente articulo. Le meticulose selection del candidatos pro le intervention chirurgic es tanto importante como le meticulose execution del operation. Patientes in le septime e octave decennio del vita pote esser operate con le mesme possibilitate de beneficio como patientes in plus juvene gruppos de etate, providite que illes es seligite de accordo con le principios describite in detalio in le texto complete del presente reporto.

Therapia chirurgic de tremor e rigiditate parkinsonian es nunc indicate a un momento relativemente precoce in le curso del morbo. Le therapia chirurgic offere le possibilitate de un rapide e frequentemente complete alleviamento de tremor, rigiditate, e deformitate e del concomitante symptomas motori de bradycinesia e de imperfection de movimento e altere functiones—in multe casos usque a un grado remarcabile. In appropriatemente seligite series, le probabilitate de effectuar tal resultatos amonta a 80 pro cento. Le mortalitate in le prime 1000 operationes consecutive esseva 2,4 pro cento. Le incidentia de hemiparesis o hemoplegia esseva levemente infra 3 pro cento.

Ben que le therapia medical merita un complete e definitive essayo in omne caso individual, le therapia chirurgic offere le sol possibilitate de non solmente abolir tremor e rigiditate sed de etiam reverter deformitates e anormalitates motori.

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THE EFFECTS OF NATURAL SLEEP AND HYPER-SOMNOLENT STATES ON RESPIRATORY FUNCTION * †

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THE close association between hypersomnolence and alterations in ventilatory function has recently received much attention. Abnormal states of somnolence associated with "central" hypoventilation have been described in a variety of conditions, such as marked obesity, 1, 2 barbiturate intoxication, 8 myotonic dystrophy 4 and encephalitis. 5, 6 In a few patients the hypoventilation phenomenon associated with somnolence has been attributed to a localized lesion in the medullary portion of the central nervous system, even though there was little evidence of neurologic illness by history or physical examination.7,8

It appeared likely that a better understanding of this problem could be obtained by a study of ventilatory function and regulation in natural sleep and hypersomnolence associated with narcolepsy. The changes observed in ventilation and blood gases in these states of consciousness are presented in this report. A study of 13 patients with narcolepsy showed that these individuals often had signs and symptoms in common with the obesitycardiopulmonary syndrome-i.e., hypoventilation, obesity, polycythemia and periodic respiration—suggesting that these two hypersomnolent illnesses may have a similar pathophysiologic disturbance in the central nervous

Relationship Between Sleep and Respiratory Control Mechanisms: Alterations in respiration during sleep have been observed for many years. The most commonly noted change has been the appearance of Cheyne-Stokes respiration, but a decrease in respiratory rate has also been found. The exact neuroanatomic and physiologic relationships between sleep and respiration, however, are not well understood. Magoun 10 and his associates have demonstrated that the area of the brain directly associated with sleep is in the diencephalon and upper brain stem. Destruction of the reticular

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formation in this area in the monkey produced the clinical and electroencephalographic changes of sleep. Stimulation of the reticular substance, on the other hand, converted the electroencephalogram of sleep to that of a waking record. It is now apparent from these and subsequent studies that sleep is due to an interruption of activating influences from the reticular pathways in the upper brain stem. It has been shown, however, that impulses from the cerebral cortex also influence the reticular substance, and any reduction of exteroceptive or proprioceptive impulses reaching the central nervous system lessens the over-all activity from either portion of this interacting system and leads to the state of sleep.

BLOOD GAS VALUES NORMAL SUBJECTS

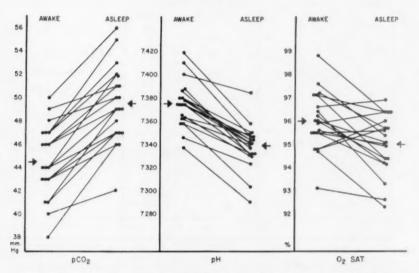


Fig. 1. Changes in arterial carbon dioxide tension, pH and oxygen saturation during sleep. The arrows indicate the mean values.

The areas of the central nervous system controlling respiration are classically located within the reticular formation of the medulla. Although stimulation of these areas near the obex has produced inspiratory or expiratory movements, these centers seemed to be controlled by pacemakers located higher in the brain stem. There is no doubt that other portions of the central nervous system, such as the uncus and the cortex of the orbitofrontal areas, also influence respiration.¹¹

In addition to these neurogenic influences, alterations in pH and blood gases are likewise important in controlling the ventilatory activity. The change in respiration produced by carbon dioxide inhalation has been known for many years, and is thought to be mediated by specific chemoreceptors in the brain stem connected with respiratory neurones. A decrease in blood oxygen concentration also influences ventilatory activity, but this effect is apparently transmitted via receptors in the aortic and carotid bodies.

Alterations in Blood Gases and Ventilation During Natural Sleep: The general depression of neuronal activity occurring during sleep is associated with a depression of ventilation. Elevation of carbon dioxide tension during sleep was first observed by Endres, 12 who attributed it, however, to an

BLOOD GAS AND VENTILATORY VALUES NORMAL SUBJECTS

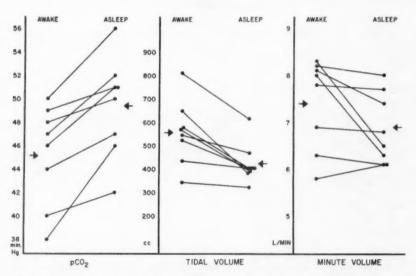


Fig. 2. Changes in arterial carbon dioxide, tidal volume and minute ventilation during sleep. The arrows indicate the mean values.

independent cyclic nocturnal variation. Studies of arterial oxygen saturation using the ear oximeter were thought to indicate a significant degree of hypoxemia during sleep, but later studies by Mangold and his associates ¹³ with direct measurements of blood gases revealed only a very slight decrease, if any, in arterial oxygen saturation. These workers also found an elevated carbon dioxide tension in fatigued subjects who fell asleep readily, but no further increase was observed during sleep itself.

Our own observations on the alterations in blood gases and ventilation during sleep have been reported elsewhere. ^{14, 15} In normal subjects, during sleep, there was an increase in the arterial carbon dioxide tension from 44.5

mm. Hg to 49 mm. Hg (figure 1). We also noted that, in the awake but fatigued individual, the carbon dioxide tension was higher than normal and the pH slightly lower. A definite decrease in arterial pH and a slight but significant reduction of arterial oxygen likewise appeared in sleep. These changes in blood gases persisted throughout sleep, varying very little with the depth or electroencephalographic stages of sleep. The blood carbon dioxide tension, pH and oxygen values returned to normal immediately on awaking. Robin and his co-workers ¹⁶ reported similar results by measuring alveolar carbon dioxide tension.

RESPIRATORY CENTER SENSITIVITY NORMAL SUBJECTS

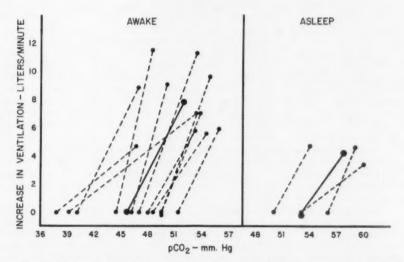


Fig. 3. Changes in ventilatory response to 5% carbon dioxide in normal subjects while awake and during sleep. Only three of the group were able to sleep during the inhalation of this gas mixture. The solid lines indicate the mean of each group.

It was postulated that the retention of carbon dioxide and the slight decrease in oxygen saturation occurring during sleep were due to hypoventilation. In our studies there was a decrease in minute ventilation from 7.4 L. a minute while the subject was awake to 6.9 L. during sleep (figure 2), whereas in Robin's subjects there was a change during sleep from 7.9 to 5.8 L. ¹⁶ A decrease in the sensitivity of the respiratory center to carbon dioxide inhalation during sleep was observed in our laboratory as well as in that of Robin and his co-workers. ^{15, 16} These workers observed that the respiratory sensitivity fell from 1.4 L./min./mm. Hg pCO₂ while awake to 0.35 L./min. during sleep. Similar evidence of a depression in respiratory

center sensitivity was found in three of our subjects who were able to sleep during the carbon dioxide inhalation (figure 3). In the remainder of our subjects this stimulus was sufficient to awaken them from sleep.

The Narcoleptic Syndrome: The clinical syndrome of narcolepsy is characterized by the tetrad of somnolence, cataplexy, sleep paralysis and hypnagogic hallucinations. ^{17, 18} It is a relatively common neurologic disorder, and is seen frequently on most neurologic services. The following two cases exemplify this syndrome:

CASE REPORTS

Case 1. A 27 year old Negro school teacher had complained of difficulty in staying awake during the day since the age of 13. At that time he had noted that he would readily fall asleep in school whenever he was not reciting aloud or moving about. This difficulty persisted throughout college and became worse upon his entering the Army. He slept a great deal during basic training, and when with the paratroopers would often fall asleep in the plane while waiting to jump. During this time he gained from 165 to 196 pounds, a weight he has maintained.

In his present position as a teacher the patient drowses frequently in the class-room, and forces himself to walk about to stay awake. He often omits lunch to take a nap, following which he is usually able to resist sleep until the end of his classes. At this time he eats a combined lunch and supper and then sleeps again for from one-half to one hour. He usually goes to bed about 10:00 p.m. His nocturnal sleep is frequently disturbed by vivid, frightening dreams which waken him several times a night. For the last five or six years he has noted that sudden emotional experiences often produce an attack of generalized weakness. During these episodes he tends to drop things, his facial muscles become weak, his knees buckle and he may fall. These sensations frequently occur while teaching, and he has to avoid becoming angry with his students. The attacks are also precipitated by other emotions, such as surprise, excitement, joy or fear. The patient states that his sister has a similar illness, and weighs more than 200 pounds.

The patient's neurologic, physical and routine laboratory examinations showed no abnormalities other than moderate obesity. The arterial carbon dioxide tension was 47 mm. Hg; pH, 7.372; oxygen saturation, 94.7%. The electroencephalogram was normal. The administration of Dexedrine did not reduce the patient's somnolence, and seemed to worsen his cataplexy. Ritalin seemed to improve his symptoms.

Comment: This patient is a classic example of the syndrome of narcolepsy with marked somnolence, cataplexy and vivid nightmares simulating hypnagogic hallucinations.

Case 2. A 59 year old white ex-patrolman complained of shortness of breath, sleepiness and of weakness spells of seven years' duration. At the onset of his illness he had been diagnosed as having heart disease. A low salt diet was prescribed, with resultant reduction of weight from 205 to 150 pounds and improvement of his symptoms. During the two years prior to hospital admission, in 1956, the patient again developed sleepiness and shortness of breath, accompanied by weight gain. On admission he weighed 175 pounds. He gave the following account of his daily activities. In the morning he would usually waken refreshed by a night's sleep, and eat a huge breakfast. In a few hours, however, he would become irresistibly sleepy, and would nap for an hour before lunch and for an equal period of time afterwards.

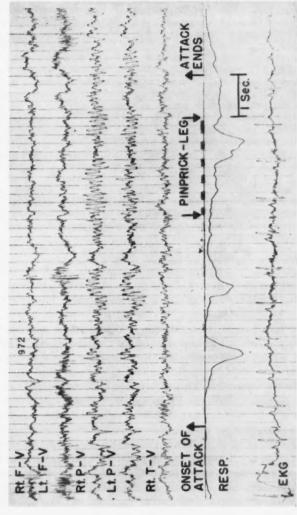


Fig. 4 The failure of painful cutaneous stimuli to abolish alpha rhythm during a cataplectic attack. Notice irregular respiratory movements during attack.

Immediately after supper, and sometimes during the meal, he would fall asleep until bedtime, when he would waken only to undress and go to bed for the night. In addition to somnolence, the patient noticed brief, transient episodes of weakness of his arms and legs. He did not lose consciousness or fall, but was unable at such times to talk clearly or to move about. During these attacks he was noted to have drooping of the eyelids, nodding of the head and jerking movements of the facial muscles. After a minute or less the patient was able to communicate, and could recall what had transpired during the spell. At first he did not connect these episodes with sudden excitement, but it soon became apparent to him that they were precipitated by laughter, surprise or anger. He seemed to have more frequent attacks while in the hospital, and these were often associated with brief encounters with his physicians, strangers, or even room-mates whom he met in the cafeteria or dining halls.

Examination failed to reveal any neurologic or physical abnormalities. The heart was not enlarged, and there was no evidence of heart failure. Laboratory findings were also normal, with left axis deviation of the electrocardiogram. The arterial carbon dioxide tension was 48.4 mm. Hg; pH, 7.271; oxygen saturation, 90%.

While in the hospital the patient's cataplectic attacks could be easily provoked. The electroencephalographic, pulse and respiratory changes of a typical episode are shown in figure 4. It should be noted that painful stimuli failed to produce blocking of alpha rhythm in the electroencephalogram during the cataplectic attack. While at rest the patient showed a typical arousal response with this stimulus. He was given a low caloric diet, with resultant loss of weight of 20 pounds but with no improvement in his symptoms. Dexedrine tended to lessen the somnolence but failed to alter the frequency of the cataplectic episodes. Phenurone, tranquilizing medications and phenothiazine derivatives were likewise unsuccessful. Indeed, the cataplectic attacks became more frequent, and at times seemed to be a conditioned response invariably occurring whenever the patient met his physician or certain other ward personnel. As many as 15 to 16 attacks occurred in a day.

In the two years since hospital discharge the patient has continued to have somnolence and cataplexy, despite a variety of medications and psychotherapeutic measures.

Comment: This patient is an example of narcolepsy in which cataplexy was the major problem. The character of the cataplectic attacks simulated focal epilepsy. They were so frequent that the patient could not find gainful employment.

The cardinal symptom of narcolepsy is the extreme somnolence. This symptom was present in all of the 13 patients in this study, and consisted of an irresistible urge to nap for frequent short periods during the day. Because of the need to remain awake while at work, or while driving a car, these patients constantly battled drowsiness and sleepiness. The circumstances which provoke drowsiness in the narcoleptic patient are the same as those which promote sleep in normal individuals, i.e., reading, attending church, viewing television and eating a large meal. The patient may feel refreshed after a few minutes of sleep, but the frequency and circumstances of his naps are often embarrassing, and may interfere with employment. Sleep often occurs while driving an automobile, and these patients have had serious accidents, or have frequently driven their cars off the road.

Cataplexy is the next most common symptom of the narcoleptic tetrad, and appeared in 10 of our 13 patients. This manifestation consists char-

acteristically of a loss of muscle tone, which may be generalized or limited to a particular region of the body. During the attacks the patient does not lose consciousness, and is aware of what is going on about him. There is often marked weakness and loss of tone of the lower limbs, and the patient may collapse to the floor. His arms fall limply at his side, and he may drop objects from his hands. Speech may become dysarthric. Ptosis of the eyelids appears, the head falls forward and the jaws loosen. The loss of muscle tone may be briefly intermittent, and if the patient makes an effort to correct his limb or head posture he may exhibit jerking movements which could be erroneously interpreted as being epileptic in nature. Situations evoking laughter are the most frequent precipitants of cataplexy, but events producing surprise, fear, excitement or anger may also be at fault. Emotions associated with meeting friends, attending the theater and playing at sports, for example, often produce cataplectic attacks which may be embarrassing to the patient.

A third manifestation of this illness is sleep paralysis, which occurred in four of our 13 patients. This symptom also appears in normal individuals, but in the narcoleptic syndrome it is quite common and is often associated with nightmares or hypnagogic hallucinations. As the patient is about to fall asleep or awaken he may find that he cannot move or cry out, even though he is awake and feels an urgent need to get up. The episode may terminate spontaneously, but is more quickly relieved if the patient is touched, moved or shaken. In some patients, sleep paralysis may be precipitated by emotional experiences in dreams and nightmares, and in this respect is similar to cataplexy. Neurologic examination of our patients during attacks of sleep paralysis or cataplexy revealed marked loss of tone of the extremities, hypoactive or absent deep tendon reflexes, and flexor or absent plantar responses.

Hypnagogic hallucinations were present in five of our patients. They consist of vivid visual or auditory phenomena which appear as the patient drowses off to sleep and are generally unpleasant or terrifying in nature. Some patients also have associated nightmares which occur during sleep itself, and the two phenomena often cannot be distinguished.

The general physical examination in the narcoleptic patient is usually normal except for evidence of obesity in some patients, and signs of hypoventilation such as plethora and Cheyne-Stokes respiration. In the majority of instances the etiology of the narcoleptic syndrome cannot be determined. In our opinion, psychogenic factors are not an important cause of narcolepsy, nor do we believe that epilepsy is a related disorder. None of our patients exhibited signs of catalepsy, i.e. ability to maintain fixed posture of their limbs for prolonged periods.

Obesity and Hypoventilation in the Narcoleptic Syndrome: Earlier studies show that approximately 50% of the patients with narcolepsy gain weight at the onset of their symptoms. In a number of instances, polycythemia was also present. The following patient with typical narcolepsy

showed, in addition, some of the symptoms and findings characteristic of the obesity-cardiopulmonary syndrome, that is, extreme obesity, polycythemia, Cheyne-Stokes respiration and a decrease in respiratory center sensitivity.

Case 3. A 50 year old laborer entered Duke Hospital in April, 1958, with the complaint of recurrent episodes of weakness of 26 years' duration. He stated that his symptoms had begun approximately six months after a blow on the head which produced unconsciousness for a half-hour. At the onset of his illness he noted that



Fig. 5. A photograph of case 3 with narcolepsy and obesity.

any sudden excitement or surprise precipitated generalized weakness. This consisted of buckling of the knees, forward flexion of the trunk and, occasionally, falling to the ground. The patient did not lose consciousness during these attacks but was unable to talk and, at times, noted quivering of the facial muscles and jerking of the head. He often pretended to be tying his shoelace whenever he fell forward as the result of sudden emotional experiences. The attacks developed with sudden emotional excitement, such as seeing an old friend, fishing and hunting, or during similar types of experiences. He recalled a particularly severe episode when his son returned unexpectedly from the armed services and he was unable to greet him because of a severe cataplectic attack. He also had attacks when he attempted to throw a rock at a strange hen or dog to frighten it from his garden.

At the onset of his illness the patient also noted considerable difficulty in staying awake, and would fall asleep as often as 25 times a day. Whenever he sat down, rested or drove a car he became extremely sleepy. At times he required four or five naps during a three- to four-hour car ride. He would sometimes fall asleep while standing or eating. Despite marked sleepiness during the day, his nocturnal sleep was disturbed because of an unexplained need to get out of bed, walk about, go to the bathroom, eat or wander about the house. During these nocturnal wanderings the patient would at times fall asleep on the toilet seat, even though he was not able

to sleep in bed.

The patient frequently observed hallucinations during the drowsy state preceding sleep at night. These were vivid, frightening experiences, and he would often climb out of bed to look about the room to determine the validity of these terrifying hallucinations. He sometimes wakened his family by his terror and screams. Often during these attacks he was unable to get out of bed or to move, even though he thought he was awake. If he was touched, shaken or moved by a member of the

family, the episode of sleep paralysis would disappear.

At the age of 32 the patient's weight increased from 155 to 322 pounds, and he was found to have diabetes. He lost weight on a low calorie diet and insulin therapy, and his weight at present is 283 pounds. He has had a rare attack of insulin hypoglycemia, which he is able to differentiate from his other attacks of weakness and somnolence. He now requires 20 units of insulin a day, but his diabetic regulation is poor. He developed gangrene of the foot due to vascular disease and uncontrolled diabetes.

On examination, the patient showed a plethoric appearance and massive obesity (figure 5). During his initial interview he developed a 15- to 30-second episode of confusion, jerking of the head and inability to speak. This was misinterpreted by the admitting intern as a petit mal or minor seizure. The routine neurologic and physical examinations were otherwise normal. Blood pressure was 170/100 mm. of Hg. The hemoglobin values ranged from 17.5 to 19 gm.%. The hematocrit was 53. The white blood count ranged from 7,500 to 9,800, with a normal differential. The fasting blood sugar was 287 mg.%. The ventilatory findings showed a tidal volume of 1.18 L.; inspiratory reserve, 2.56; expiratory reserve, 0.89; vital capacity, 120%; maximal breathing capacity, 73% of predicted values. The oxygen saturation was 89-91%, carbon dioxide tension 45.8 mm. Hg and pH 7.376. There was Cheyne-Stokes respiration, and the respiratory center sensitivity to carbon dioxide stimulus was slightly decreased, with a value of 0.8 L. per minute per mm. Hg rise in pCO₂.

Comment: This patient illustrates some of the combined symptoms of narcolepsy and the obesity-cardiopulmonary syndrome. Although such patients may gain sufficient weight during their narcoleptic illness to develop the picture of Pickwickian syndrome, it appears more likely that a common neurogenic factor is responsible for both conditions.

Manifestations of the obesity-cardiopulmonary syndrome were observed in several of our 13 patients with narcolepsy. Nine of them were obese, with weights varying from 185 to 375 pounds. Two patients had Cheyne-Stokes respiration, and three had polycythemia. Two of them also had a history of congestive heart failure several years previously, but were well compensated on admission to this hospital. There were no electrocardiographic abnormalities. Cyanosis was likewise absent. Contrary to the observations in the obesity-cardiopulmonary syndrome, loss of weight did not usually decrease the degree of somnolence in the patients with narcolepsy (figure 6).

Eight of our 13 patients who were studied more completely showed evidence of hypoventilation as seen in normal sleep. While awake, the nar-

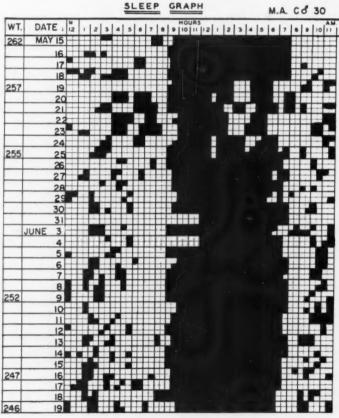


Fig. 6. Failure of weight loss to alter sleep habits of a patient with narcolepsy and obesity. Patient weighed 280 pounds on admission to the hospital. Each small block represents 15 minutes.

BLOOD GAS VALUES

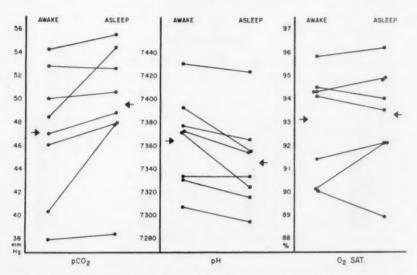


Fig. 7. Changes in arterial carbon dioxide tension, pH and oxygen saturation in narcoleptic patients. The arrow indicates the mean values in each state of awareness.

coleptic patients showed evidence of a depression of ventilation, with a mean resting arterial carbon dioxide tension of 47 mm. Hg, a value significantly higher than that found in normal control subjects (figure 7). The arterial pH and oxygen saturation were also lower than normal, with mean values of 7.366 and 93%, respectively. These alterations in blood gases are not so marked as those found in the obesity-cardiopulmonary syndrome, but approach those seen in the normal subjects while asleep. During sleep there was only a very slight elevation of pCO₂, with a slight decrease in pH, but these changes were not so great as those observed in normal subjects.

There was a decrease in vital capacity and maximal breathing capacity in this group of narcoleptic patients, but the reduction was not so great as that seen in the obesity-cardiopulmonary syndrome (figure 8). The other ventilatory studies, such as residual capacity and expiratory reserve, were normal.

The response of the respiratory center to carbon dioxide inhalation in the patients with narcolepsy showed a slight but not significant reduction from the normal, with a mean value of 0.87 L. per mm. Hg rise in pCO₂ (figure 9). This decrease in the respiratory center sensitivity in the narcoleptic patient while awake was quite similar to the value of 0.81 L. observed in the normal subject while asleep, but considerably less than the markedly

PULMONARY FUNCTIONS

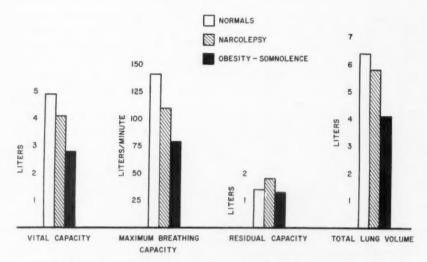


Fig. 8. The relationship between the mean values for pulmonary function and lung volumes in young normal subjects, narcoleptic patients, and those with obesity-cardiopulmonary disease.

RESPIRATORY CENTER SENSITIVITY

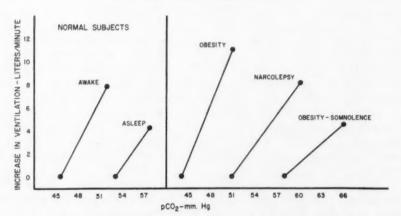


Fig. 9. The ventilatory response to carbon dioxide in normal subjects while awake and asleep, and in patients with obesity, narcolepsy and with obesity-cardiopulmonary syndrome.

depressed values (0.5 L.) found in the obesity-cardiopulmonary syndrome. Obesity per se does not alter this function, since a group of obese patients without evidence of somnolence had a normal response to carbon dioxide inhalation.¹⁰

Discussion

These data suggest that sleep and hypersomnolent states have a profound influence on respiratory function. Not only is there depression of respiratory center sensitivity in natural sleep, but there is also evidence of hypoventilation in patients with narcolepsy while awake. It would appear that the respiratory center is normally dependent upon a constant input of sensory impulses to maintain optimal function. In the narcoleptic patient, either there are fewer afferent stimuli associated with decreased awareness, or

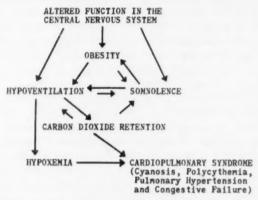


Fig. 10. Possible mechanisms in the pathogenesis of the obesity-narcolepsyhypoventilation syndrome.

there is a decreased responsiveness of the nervous system to these impulses. Our observation that painful, cutaneous stimuli in the cataplectic state fail to block the alpha rhythm in the electroencephalogram is compatible with the latter concept. The disturbances in central nervous system function in narcolepsy, and probably the somnolence and hypoventilation as well, are in most cases the result of an alteration in neurophysiologic mechanisms, rather than a specific pathologic lesion. Neither the neuronal pathways nor the nature of the altered function producing this syndrome is understood, but they must involve, among other structures, the respiratory control centers as well as sleep mechanisms.

Cases of "central" hypoventilation are now being reported with increasing frequency. Various neurologic lesions in the region of the medullary respiratory center have been postulated as the basis for the disorder. These patients usually show no other neurologic signs, but in a few instances there

was evidence of cerebral thrombosis, parkinsonism or encephalitis. A reduction in awareness or somnolence per se is not necessarily associated with a depression of respiratory function. Indeed, in some cases of brain stem infarction, and in patients with bilateral cortical lesions, the opposite effect—i.e., hypocapnia and increased respiratory center sensitivity—has been observed.²⁰ It would therefore appear that specific alterations in neurophysiologic function are necessary to produce the syndrome of somnolence and

hypoventilation.

The possible interrelationships between obesity, somnolence and hypoventilation in narcolepsy are shown in figure 10. In all probability the sleepiness and hypoventilation are caused by an alteration in central nervous system function. The obesity may be due to a psychologic mechanism, or may be the result of inactivity associated with somnolence. However, the frequent occurrence of obesity in narcoleptic patients, and the rapid gain of weight of 50 to 100 pounds sometimes observed in the first year of this illness, suggest an organic mechanism. Lesions of the hypothalamus and other areas of the brain are known to produce polyphagia and obesity in experimental animals as well as in patients. Polyphagia and somnolence, for example, are the cardinal symptoms of the Kleine-Levin syndrome, 21 some instances of which are thought to be postencephalitic in origin. On the other hand, patients with narcolepsy rarely if ever manifest other signs of hypothalamic involvement—i.e., diabetes insipidus or other endocrine disturbances—and a lesion of the hypothalamic area would appear to be unlikely. Regardless of its etiology, the incidence of weight gain in narcolepsy is too frequent to be considered an incidental finding.

The degree of obesity usually found in the narcoleptic patient is not so severe as that in the Pickwickian syndrome, and would not account for marked alterations in pulmonary function unless accompanied by a certain degree of somnolence. The retardation of chest wall movements by adipose tissue may contribute to the somnolence, since the proprioceptive stimuli of respiratory movements could have an alerting effect in an otherwise resting subject. This increase in somnolence may in turn produce further diminution of respiratory excursions and establish the cycle of events seen in the obese narcoleptic with hypoventilation. In extreme cases the hypoxemia, retention of carbon dioxide and polycythemia increase pulmonary arterial pressure, all of which may contribute to cardiac enlargement and heart failure.

The degree of arterial carbon dioxide retention and the slight decrease in oxygen saturation observed in sleep and in the narcoleptic patient while awake would not of themselves be expected to produce sufficient depression of the central nervous system to promote sleep. Indeed, higher levels of CO₂ retention are known to occur in patients with chronic lung disease without producing hypersomnolence. However, a moderate increase in carbon dioxide tension in a patient with encephalitis has been observed to produce the electroencephalographic changes and clinical signs of sleep, manifesta-

tions which were usually reversed by hyperventilation.⁵ Similarly, in narcolepsy and in the Pickwickian syndrome, retention of carbon dioxide may aggravate the existing somnolence.

SUMMARY

Natural sleep and the hypersomnolence of narcolepsy are associated with a depression in respiratory function which results in a slight decrease in arterial oxygen saturation, retention of carbon dioxide and decreased sensitivity of the respiratory center to carbon dioxide stimulus. Patients with narcolepsy may also manifest obesity, Cheyne-Stokes respiration, polycythemia and other signs of the hypoventilation-cardiopulmonary syndrome. It is suggested that some narcoleptic patients represent "formes frustes" of the Pickwickian syndrome, and that these two conditions, as well as certain instances of primary hypoventilation, have a common neurogenic factor.

ACKNOWLEDGMENT

We are indebted to Mrs. Mary Pike, Mrs. Mary Ruth Greenfield and Miss Corinna Thomas for their valuable technical assistance.

SUMMARIO IN INTERLINGUA

Le alterationes del function respiratori que occurre in somno natural e in statos de hypersomnolentia esseva studiate in subjectos normal e in 13 patientes con narcolepsia, incluse novem qui esseva obese, con pesos de inter 185 e 375 libras. Le diagnose de narcolepsia esseva supportate per le presentia de hypersomnolentia e cataplexia concomitante, hallucinationes hypnagogic, o episodios de paralyse al tempore del addormir se. Duo del patientes habeva etiam respiration de Cheyne-Stokes, e tres habeva polycythemia. Alterationes del gases in le sanguine arterial, del ventilation, e del sensibilitate del centro respiratori esseva correlationate con le alterationes del activitate electroencephalographic observabile in statos de somnolentia e de somno profunde.

In subjectos normal, retention de dioxydo de carbon e leve reductiones del contento de oxygeno esseva observate in le sanguine arterial al tempore del prime alterationes electroencephalographic de somnolentia, e iste alterationes persisteva durante le periodo de somno complete. Le sensibilitate del centro respiratori esseva etiani reducite levemente durante le somno. In le stato eveliate le patientes narcoleptic tendeva a monstrar pro le gases del sanguine e pro le sensibilitate del centro respiratori valores simile a illos notate in subjectos normal addormite. Iste studios suggere que patientes narcoleptic suffre in lor stato eveliate de disturbationes functional in le systema nervose central de character simile a lo que occurre in subjectos normal quando illes dormi. Le obese patientes narcoleptic habeva retention de dioxydo de carbon, reduction del saturation oxygenic, e alterationes pulmono-functional de character simile (ben que de grados de severitate inferior) a lo que es observate in le syndrome cardio-pulmonar de obesos.

Es discutite le relation possibile inter obesitate, somnolentia, e hypoventilation in casos de narcolepsia. Es postulate que certe patientes narcoleptic representa un forma de syndrome obeso-cardio-pulmonar o pickwickian. Il pare que le duo conditiones ha in commun un factor neurogene que es responsabile pro le presentia de somnolentia e possibilemente del depression del centro respiratori e etiam del

obesitate.

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RENAL INVOLVEMENT IN PROGRESSIVE SYSTEMIC SCLEROSIS (SCLERODERMA) *

By Robert I. Levine, M.D., Boston, Massachusetts, and Buris R. BOSHELL, M.D., Birmingham, Alabama

RENAL involvement in progressive systemic sclerosis has been recognized for many years. As Osler 1 observed, "The patients are apt to succumb to pulmonary complaints or to nephritis." More recently, even though this complication has received increasing attention in the literature, it frequently has been ignored. This fact prompted the authors to report the recent experience with this lesion at the Peter Bent Brigham and Robert Breck Brigham Hospitals.

The classic picture of sclerodermatous involvement of the skin has been well known for many years. During the last 20 years, however, as the systemic manifestations have become the object of more intensive study, it has become apparent that any organ system of the body may be involved.²⁻⁷ In recognition of this, Goetz a suggested that progressive systemic sclerosis would be a more suitable name than scleroderma, which bears the connotation of primary—if not only—skin involvement. Because it is our intention to discuss chiefly the renal involvement in the following case reports, other important and interesting manifestations will be dealt with only in passing.

CASE REPORTS

Case 1. A 43 year old white unmarried salesgirl had been in excellent health until one year prior to her admission to the Peter Bent Brigham Hospital, at which time she consulted a physician with the chief complaint of oliguria. She was allegedly told that her tissues were diseased. A record of that visit is not available. In April, 1958, she began to complain of swelling and stiffness in her hands and arms. Her face was noted to be reddened, and her gait became stiff and awkward.

She was admitted to a Providence, Rhode Island hospital on June 24, 1958, for evaluation and treatment of the above complaints. There she was found to have the classic physical findings of scleroderma. Her temperature was 99.6° F.; pulse, 100; respiration, 20; blood pressure, 170/90 mm. of Hg.

Laboratory data included a blood urea nitrogen of 15.8 mg.%, negative urine except for a trace of protein, and a serum protein of 6.5 gm.%, with a normal ratio of albumin to globulin (A/G ratio). The serum cholesterol, blood sugar, icteric index, C-reactive protein, L.E. cell preparation and antistreptolysin titer were all within normal limits. The electrocardiogram and chest x-ray were normal.

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ham Hospital, 721 Huntington Avenue, Boston 15, Massachusetts.

The patient's blood pressure began to climb while she was in the hospital, and reached a high of 250/140 mm. of Hg. She was started on Serpasil and Diuril, and the pressure fell to 130/100 mm. of Hg. Convulsions began on July 6, and the patient complained of a severe frontal headache. A lumbar puncture performed at this time was normal except for a total protein content in the spinal fluid of 85 mg.%. The patient became progressively more somnolent and confused. Her urine volume was noted to be small, and on July 15 she became anuric.

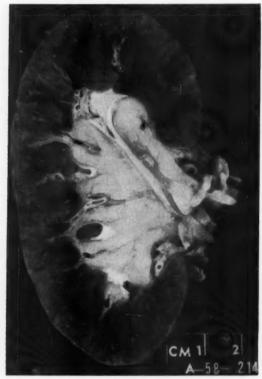


Fig. 1. Case 1. Cut surface of kidney, showing the typical appearance of the gross renal lesion. There are multiple subcapsular hemorrhages and infarctions. In the cortex are multiple petechiae and gray and red streaks.

She was transferred to the Peter Bent Brigham Hospital on July 16. On admission she was a moribund middle aged woman with the typical skin changes of scleroderma. Her blood pressure was 200/100 mm. of Hg; pulse, 80; respiration, 36. She was disoriented, but responded to verbal commands and noxious stimuli. There were bilateral extensor plantar responses. Laboratory data included a urine with 2 plus protein, an occasional white blood cell, and many hyaline and granular casts. Her hematocrit was 26%; white blood count, 17,400, with a normal differential; blood urea nitrogen, 148 mg.%; total protein, 6.1 gm.%, with normal A/G ratio. The fasting blood sugar was 104 mg.%. Other chemical tests included a

serum cholesterol of 180 mg.%; sodium, 127 mEq./L.; potassium, 5.1 mEq./L.; CO₂ combining power, 5.0 mM./L.; chloride, 84 mEq./L.; calcium, 4.4 mEq./L.; phosphorus, 3.0 mM./L.; alkaline phosphatase, 2.0 Bodansky units; bilirubin, 0.38 mg.%; lactic dehydrogenase, 750 units (normal, 100 units); uric acid, 20.2 mg.%.

An electrocardiogram was within normal limits. Chest x-ray demonstrated

changes consistent with early congestive heart failure.

The patient was completely anuric except for about 20 ml. of urine, obtained by catheterization at the time of admission. She had a temperature of 102.6° F., which diminished with parenteral antibiotics. Retrograde ureteral catheterization demonstrated no obstruction, and a flat film of the abdomen showed slightly small kidney shadows. The patient was placed on an anuric regimen of 500 ml. of 50% dextrose in water per day; sodium bicarbonate, 88 mEq. per day for two days, and sodium cycle cation exchange resins. On this program her serum potassium remained normal; however, she became progressively more uremic, and died on the eighth hospital day.

At necropsy the kidneys weighed 88 and 93 gm., respectively. The capsule stripped with ease to reveal multiple subcapsular hemorrhages and infarctions. The cortices contained multiple gray and red streaks and petechiae. Microscopically, the intra-lobular arteries were most involved, with marked fibrinoid necrosis of the media and intimal proliferation. Proliferation of the intima was also seen in the interlobular arteries. Large areas of cortical necrosis and polymorphonuclear leukocytic and fibroblastic infiltration were found. Within the collecting tubules there were many

hvaline and white blood cell casts.

Similar vascular changes were noted to a marked degree in the pancreas, and to a moderate degree in the spleen and liver. Lesions characteristic of progressive systemic sclerosis were found in the lungs and skin. There was a small superficial

healing gastric ulcer.

Case 2. A 58 year old white male construction worker was admitted to the Peter Bent Brigham Hospital on October 25, 1955, with the chief complaint of swelling and stiffness of his hands and, to a lesser degree, of his feet, of one year's duration. His other complaints were easy fatigability, mild dyspnea on exertion, occasional ankle edema, and a 40-pound weight loss over this same period of time. He had had moderate hypertension for at least four years, and had experienced two mild episodes of epistaxis during the three days prior to admission. His ethanol consumption had been high until one year prior to admission. Treatment had included a short course

of prednisone in January, 1955, with transient relief.

On admission the patient was a stocky, florid-faced man who appeared older than his stated age. Temperature, 98° F.; pulse, 90; respiration, 20; blood pressure, 200/110 mm. of Hg. There were typical severe sclerodermatous changes in the skin of the hands, forearms and face, with loss of skin appendages and ulcerations over the fingers. The sclerae were faintly icteric. The fundi contained arteriosclerotic changes, and several flame-shaped hemorrhages and exudates. The discs were flat. The neck veins were slightly distended. The chest was resonant, with poor diaphragmatic excursions, and there were râles at both bases. The heart was not enlarged to percussion; M_1 was split, and A_2 had a tambour-like quality. No murmurs, rubs or gallops were detected. The liver edge was palpable 6 cm. below the right costal margin, and the spleen tip was felt at the left costal margin. There was a trace of pedal and ankle edema.

Laboratory data included a hematocrit of 39%, white blood cell count of 12,000, with 87% neutrophils. The urine specific gravities varied from 1.011 to 1.016, with 1 plus protein, no sugar, and a sediment that contained 0 to 8 red blood cells and 45 to 60 white blood cells per high power field. There were occasional hyaline and granular casts. Stool benzidine test was 2 plus, and the blood Hinton test was nega-

tive. Other chemical results were: blood urea nitrogen, 99 mg.%; fasting blood sugar, 112 mg.%; serum protein, 6.3 gm.%; albumin, 3.8; globulin, 2.5; CO₂ combining power, 18.9 mM./L.; cholesterol, 229 mg.%; sodium, 133 mEq./L.; potassium, 4.3 mEq./L.; bilirubin, 3.35 mg.%; alkaline phosphatase, 1.5 Bodansky units; thymol turbidity, 55 units (normal, up to 40); calcium, 5.1 mEq./L.; phosphorus, 4.5 mM./L.; uric acid, 16.9 mg.%; prothrombin time, 70%; venous pressure, 62 mm. of saline; circulation time (Decholin), 17 seconds. The electrocardiogram showed low voltage and failure of R wave progression across the precordium. Radiologic examination demonstrated decreased cardiac pulsation and bilateral pleural thickening. There were increased bronchovascular markings. On barium swallow there was no esophageal peristalsis and delay of passage was noted at the lower third of the organ. In the hands there were demineralization of the phalangeal bones and minor hypertrophic changes, with soft tissue calcification of one finger.

During his hospital course the patient showed signs of congestive heart failure, decreased pulmonary ventilation, hepatic failure and azotemia. His urine output fell to 600 c.c. on his third hospital day, and progressively decreased to 160 c.c. on the day prior to his death. Venous pressure rose to 140 mm. of saline, blood urea nitrogen to 253 mg.% and serum potassium to 6.6 mEq./L., while the CO₂ combining power fell to 10 mM./L. This acidosis remained refractory to therapy. Antibiotics and hydrocortisone were given without effect. During his last few hospital days the patient developed bilateral pleural effusions and became comatose. His blood pres-

sure slowly fell, and he died on the twelfth hospital day.

At necropsy the kidneys weighed 190 and 160 gm. The capsules were thickened and stripped with ease to reveal a pale red-brown granular surface. There were fine linear white markings and small petechiae in the cortices. The medullae were densely striated. Microscopic examination demonstrated prominent intimal proliferation of the intralobular arteries, and medial fibrinoid degeneration of the afferent arterioles. There were many small, wedge-shaped, radially arranged cortical infarcts. In many glomeruli there was slight basement membrane thickening, and some had fibrin thrombi obliterating portions of the glomerular tufts. There was hydropic degeneration of many of the tubular epithelial cells.

Additional findings included sclerodermatous involvement of the skin and esophagus, interstitial myocardial fibrosis, acute fibrinous pericarditis, and moderate pulmonary atherosclerosis with acute and organizing bilateral bronchopneumonia. There were portal cirrhosis, acute ulcerative duodenitis and focal testicular fibrosis.

Case 3. A 50 year old white male was referred to the Peter Bent Brigham Hospital on September 13, 1958, for progressive uremia, loss of visual acuity and exertional dyspnea. He had been in apparent good health until 1956, when intermittent swelling and stiffness of the hands and ankles were first noted. Five weeks prior to admission he had an acute episode of anterior chest pain, and was hospitalized and treated for acute myocardial infarction. At this time his systolic blood pressure was noted to be above 200 mm. of Hg. On September 3 he developed progressive visual loss, dark urine and weakness. Azotemia, anemia, hematuria, proteinuria and cylindruria were noted by his physician, who referred him to this hospital after two blood transfusions. At the time of admission he developed epigastric "hunger pains," which were relieved by milk.

On admission the patient was a well developed, cachectic, disoriented, semistuporous man with a blood pressure of 168/102 mm. of Hg; pulse, 102; respirations, 18; temperature, 98.4° F. There were typical early sclerodermatous changes in the hands and forearms. In the ocular fundi there were severe hypertensive changes, with hemorrhages, exudates and papilledema. Heart and lung examination revealed cardiomegaly and signs of congestive heart failure. The liver was percussed 8 to 10 cm. below the right costal margin. Slight pitting sacral edema was present. Laboratory data included a urine pH of 4.5, specific gravity of 1.010, protein of 2 plus, and a sediment that contained 40 red blood cells, 5 to 6 white blood cells, and many hyaline and granular casts per high power field. The hematocrit was 29% and the white blood cell count was 20,000, with neutrophils predominating. The blood urea nitrogen was 50 mg.%; calcium, 3.9 mEq./L.; phosphorus, 3.6 mM./L.; alkaline phosphatase, 5.8 Bodansky units. The serum sodium was 137 mEq./L.; potassium, 2.3 mEq./L.; carbon dioxide combining power, 18.4 mM./L.; chloride, 92 mEq./L.; bilirubin, 1.21 mg.%; uric acid, 18 mg.%. The stool benzidine was 1 plus; prothrombin time, 70%; clotting time, 11 minutes; bleeding time, 2 minutes.

The electrocardiogram showed tall broad P waves, and evidences of left and right ventricular hypertrophy. Radiologic examination of the chest demonstrated a markedly enlarged heart with pulmonary vascular engorgement and bilateral small pleural effusions. No renal shadows were observed on flat film of the abdomen. Retrograde urography showed no obstruction and normal configuration of the renal calyces. Raynaud's phenomenon was demonstrated by immersing the patient's hand in iced water.

TABLE 1 Clinical Data

| Case No. | Age | Sex | Blood Pressure | Terminal Blood Urea Nitrogen (mg. %) | Duration of PSS Prior to Clinical Renal Involvement | Duration of Life After Clinical Onset of Acute Renal Lesion |
|----------|-----|-----|-------------------|--|---|---|
| 1 | 43 | F | 250/140 | 148 | 1 year | 30 days |
| 2 | 58 | М | 200/110 | 253 | 1 year | 16 days |
| 3 | 50 | M | 168/102 | 180 | 2 years | 17 days |
| 4 | 28 | F | 140/90 | 121 (NPN) | 20 months | 17 days |
| 5 | 59 | M | 190/110 | 133(NPN) | 23 years before onset of acute lesion | 20 days |

His hospital stay lasted only five days. During this period his renal output fell to 250 ml. per 24 hours, serum sodium to 128 mEq./L., and CO $_2$ combining power to 16.1 mm./L., while his blood urea nitrogen rose to 180 mg.%, and potassium to 4.0 mEq./L. The patient was maintained on a strict anuric regimen, with treatment directed at maintaining a low serum potassium and high pH.

On the fifth hospital day the patient was discharged against advice in accordance with the wishes of his wife. He died at his home in Maine two days later. Necropsy was not performed.

Case 4. A 28 year old white female professional dancer was admitted to the Robert Breck Brigham Hospital on December 27, 1957, for the third time for management of an acute exacerbation of joint symptomatology. She had been known to have had scleroderma of her upper extremities, face and thorax for about 20 months, presenting as or coincidentally with toxemia of pregnancy. Eight days prior to this admission she had developed severe supraorbital pounding headaches, nausea, vomiting and progressive weakness. Earlier she had observed Raynaud's phenomenon, but no other symptoms of systemic disease. She had never received steroid therapy.

In December, 1956, the patient's urine was first noted to contain 2 to 3 plus protein. Her blood pressure was consistently recorded in the area of 120/80 mm. of Hg, and in September, 1957, her nonprotein nitrogen was 21 mg.%.

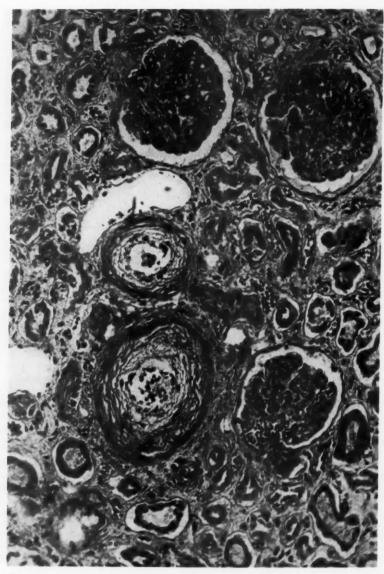


Fig. 2. Case 4. Microscopic area of kidney, showing typical vascular lesions. In the intralobular arteries there are intimal hyperplasia and slight fibrinoid necrosis of the media. Fibrinoid necrosis is seen in the afferent arterioles. (See also the text.) Hematoxylin and eosin stain. Magnification $430 \times$.

On admission the patient was a well developed, moderately cachectic, deeply pigmented, lethargic white woman complaining of joint pain in her hands. Her temperature was 99° F.; pulse, 120; blood pressure, 140/90 mm. of Hg; respiration, 22. There was mild retinal arteriolar tortuosity. There were typical sclerodermatous changes of the skin of her face, hands, thorax and abdomen. Expansion of the chest with respirations was very limited, and breath sounds were barely audible. The heart was slightly enlarged. A grade 2, soft, blowing systolic murmur was best heard at the apex. Abdominal and neurologic examinations revealed no abnormalities. There was no peripheral edema.

Laboratory data included a urine with a specific gravity of 1.017, and 4 plus protein. The sediment contained a few red blood cells per high power field, and many hyaline and finely and coarsely granular casts. On the day of admission the hematocrit was 38.5%; white blood cell count, 14,800, with a shift to the left; non-protein nitrogen was 121 mg.%; serum sodium, 136 mEq./L.; potassium, 4.0 mEq./L.; CO₂ combining power, 17.7 mM./L.; chloride, 95 mEq./L. Latex fixation and fluorescent antibody tests were positive. Chest x-ray showed bilateral small pleural effusions and increased pulmonary markings. Nonspecific ST-T changes were found on the electrocardiogram.

TABLE 2
Organ Involvement at Necropsy

| Case | Skin | Esophagus | Heart | Lungs | Kidney | Pancreas | Other |
|------|--------|-----------|----------|----------|--------|----------|---|
| 1 | Severe | No | Minimal | Moderate | Severe | Severe | Spleen, moderate Liver, moderate |
| 2 | Severe | Severe | Moderate | Moderate | Severe | Mild | Testicular, moderate Small intestine, moderate |
| 4 | Severe | Severe | Moderate | Moderate | Severe | Moderate | Adrenals, severe Posterior pituitary, moderate Larynx, severe |
| 5 | Severe | Severe | Moderate | Severe | Severe | Severe | Adrenals, moderate Spleen, moderate Testicular, severe Small intestine, severe Parathyroid, hyperplasia |

The patient's hospital course was marked by persistent oliguria in spite of adequate hydration. Treatment consisted of digitalization, cortisone and antibiotics. Her temperature rose to 101° F. She became disoriented, and developed a pericardial friction rub. Terminally she developed evidence of pulmonary consolidation, uremia and congestive heart failure, and died on the ninth hospital day.

At necropsy the kidneys each weighed 160 gm. The capsule stripped with ease, uncovering a fairly smooth surface with few infarcts. On the cut surface likewise there were few areas of necrosis or petechiae. Microscopically, there were marked intimal proliferation of the interlobular and intralobular arteries, and fibrinoid necrosis of the media of the afferent arterioles. A few areas of cortical infarction were observed. The glomerulocapillary basement membranes were thickened to a variable degree and were focally fused. In a few glomeruli, large portions of the tufts were replaced with an amorphous, dull, eosinophilic material. Beneath the capsule, groups of atrophic tubules alternated with hypertrophic ones. Moderate numbers of hyaline casts were present, and many of the tubular epithelial cells were infiltrated with fat.

Additional findings included the typical changes of progressive systemic sclerosis in the skin, esophagus and lungs. There were moderate interstitial myocardial fibrosis and fibrinous pericarditis. Vascular lesions similar to those found in the kidney were observed in the lungs, pancreas, liver and adrenals. There were focal necrosis of the posterior pituitary, ulcerative laryngitis, bronchopneumonia and an acute duodenal peptic ulcer.

Case 5. A 59 year old male shopkeeper was admitted to the Robert Breck Brigham Hospital for the fourth time on December 17, 1958. He had been ill since 1935, when he had developed Raynaud's phenomenon. In 1945 he began to develop skin

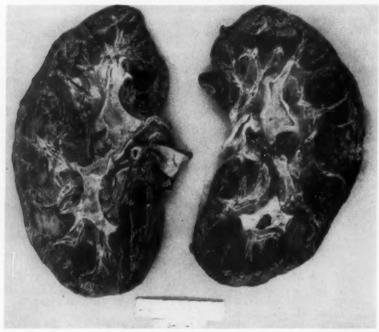


Fig. 3. Case 5. Cut surface of kidney, showing the acute lesion of progressive systemic sclerosis superimposed upon chronic renal disease. The surface is finely nodular, with several deep scars. The cortex is thin. There are multiple punctate hemorrhages and gray and yellow streaks.

and joint changes in his hands that were typical of scleroderma. In 1953 he was first seen at this hospital, and was noted to have a blood pressure of 130/80 mm. of Hg and a normal, protein-free urine. Since there was evidence of esophageal involvement and ulcerations of the fingers, he was started on cortisone. In 1954, sympathetic block was executed, with satisfactory symptomatic relief. He was treated intermittently with moderate doses of prednisone for the next two years. In August, 1955, his urine became positive (3 plus) for protein, and his blood pressure rose to 140/90 mm. of Hg. In 1956 he was given a course of Releasin therapy, without relief. His blood pressure had risen to 200/120 mm. of Hg, but with steroid withdrawal and antihypertensive treatment it fell to 150/95 mm. of Hg. His urine specific gravity became fixed between 1.007 and 1.012. In May, 1958, his urine protein became 4

plus and his blood pressure was 160/90 mm. of Hg. Blood nonprotein nitrogen was 37 mg.%, and a fluorescent antibody test was positive.⁸ Latex fixation was negative, but positive latex inhibition was demonstrated. Digitalization produced no apparent relief of his shortness of breath.

On admission the patient was an emaciated man who appeared to be acutely ill. Temperature, 97° F.; pulse, 70; respiration, 24; blood pressure, 190/110 mm. of Hg. There were typical scleroderma lesions on his upper extremities, face and thorax. His pupils were miotic, and the ocular fundi could not be visualized. The neck veins were moderately distended. There were moist râles at both lung bases. The heart sounds were distant. A grade 2, soft, systolic murmur was best heard at the left sternal border. Flexion contractures of all extremities existed, and no deep tendon reflexes could be elicited.

Laboratory data included a urine specific gravity of 1.012, 4 plus protein, and a pH of 5.0. The sediment contained one to three white cells per high power field, and a few red cells. Many hyaline and granular casts were present. Hinton test was negative. The hematocrit was 36%; white blood cell count, 16,500, with a marked shift to the left; nonprotein nitrogen, 55, rising to 133 by December 29. The fasting blood sugar was 58 mg.%. X-ray of the chest was reported as consistent with congestive heart failure.

The patient's hospital course consisted of progressive oliguria, azotemia, congestive heart failure and coma. He had several hypoglycemic episodes, promptly relieved with intravenous glucose. His fluorescent antibody test remained positive in spite of treatment with intravenous D-N-A Histone. His urine output varied from 675 c.c. to 175 c.c. per day, and he died in coma on January 2, 1959, having put out no urine in the last 36 hours of his life.

At necropsy the kidneys weighed 120 and 135 gm. The capsule was firmly adherent to the finely nodular and deeply scarred surface. The cut surface of the kidney exhibited many punctate hemorrhages and gray and yellow streaks. The cortex was thin. Microscopically, the vascular lesions of intimal hyperplasia and medial fibrinoid necrosis were present in the intralobular arteries and afferent arterioles. There were multiple small cortical infarcts. In addition to this, there were many hyalinized glomeruli, and large areas of fibrosis and lymphocytic infiltration. There was medial calcification of many of the larger arteries.

Additional findings included the typical lesions of progressive systemic sclerosis in the skin, lungs, esophagus and skeletal muscle. Vascular lesions similar to those found in the kidney were observed in the spleen, pancreas, adrenals and many other areas. There were moderate parathyroid hyperplasia and areas of metastatic calcification throughout the body, with striking calcium deposits in the walls of many of the larger arteries. In the heart there were interstitial fibrosis and a small, fresh anteroseptal myocardial infarct. There were testicular atrophy, acute pseudomembranous colitis and large areas of necrosis and calcification in the jejunum.

DISCUSSION

Renal involvement in progressive systemic sclerosis is not an unusual occurrence. Most large series of cases report a very high incidence of histologic renal involvement, and in a substantial percentage the renal lesion dominates the clinical picture. Piper and Helwig,⁶ in their report of 31 autopsied cases, found histologic evidence of renal involvement in 30. Clinical evidence of renal disease was present in 24. Five died of acute renal failure and two of malignant hypertension. These figures seem to be repre-

sentative. Our small series is unsuitable for drawing conclusions on the incidence of renal involvement, particularly since two of them (cases 1 and 3), were referred specifically for management of their renal failure. It is of interest to note, however, that the two Robert Breck Brigham Hospital cases are the only two fatal cases of progressive systemic sclerosis at that institution in the time interval covered (1955–1958).

Clinically, the renal lesion may run a benign, protracted course or, more commonly, an acute, rapidly fatal one. It may intervene at any point in the course of the disease; in fact, in some it may even occur before the skin changes have become diagnostic.⁶ The acute form is characterized by the rapid onset and progression of either acute renal failure with azotemia, or malignant hypertension, or, more commonly a combination of both.⁹⁻¹⁶ The chronic renal lesions are frequently subclinical, and usually manifest themselves as an incidental finding of proteinuria or an abnormal urinary sediment. These patients may be hypertensive, but azotemia is not often observed. Rarely, gitter cells are seen in the absence of pyelonephritis.¹⁰ Some of the patients have developed the nephrotic syndrome.¹⁷ Patients with the chronic form are not infrequently observed to change abruptly to the acute renal form, as did our case 5.

Histologically, many different lesions have been observed in conjunction with progressive systemic sclerosis, although in most reported cases a triad predominates: (1) intimal proliferation of the small intralobular arteries and arterioles; (2) fibrinoid necrosis involving the walls of the afferent arterioles and sometimes the glomerular loops; (3) focal cortical infarctions. This triad seems to be characteristic of progressive systemic sclerosis, 10, 13 and was observed in our four autopsied cases. There is some controversy as to the significance and specificity of these lesions. Fisher and Rodnan 12 were able to demonstrate no significant morphologic or tinctorial difference between these lesions and those found in the kidneys of patients dying from essential malignant hypertension. Although it has been suggested that the renal lesion associated with this disease is secondary to hypertension, some cases 10, 11, 13 have developed the renal lesion without an elevated blood pressure. Our case 4 is an example of this. Calvert and Owen, 13 on the other hand, state that the lesion is specific, and that a pathologist can diagnose progressive systemic sclerosis with no knowledge of the case other than his observation of the typical renal lesion.

In the cases that run a more chronic course there is evidence of long-standing renal damage, such as glomerular hyalinization and interstitial fibrosis, ^{6, 18} as in our case 5.

Lesions considered to be specific for other diseases have been described in occasional cases of progressive systemic sclerosis. These have included vascular lesions simulating periarteritis nodosa, 14, 19 wire-loop lesions typical of disseminated lupus erythematosus, 5 glomerular crescents, as in glomerulonephritis, 18 and nephrocalcinosis. 20 It is difficult to explain these observa-

tions except by the commonly recognized overlap in the manifestations of the various collagen-vascular diseases.

The prognosis of the progressive systemic sclerosis patient with the acute renal lesion is very poor. The life expectancy in reported cases after the onset of oliguria and azotemia varies from five days to seven weeks. Our cases all fell within this range. This relentless progression of renal failure seems to be little if at all affected by any currently available form of treatment. In fact, it has been suggested that antihypertensive agents may aggravate or precipitate the renal failure. It has also been suggested that adrenal steroid or ACTH administration may be harmful. These drugs have been thought to elevate the blood pressure, and perhaps either to induce or to accelerate pre-existing renal vascular lesions. It is unlikely, however, that the prevalent use of corticosteroids in progressive systemic sclerosis is responsible for all of these renal lesions, since some reported cases, 4, 13, 16 and our cases 1, 3 and 5, developed typical lesions without having taken these hormones within at least six months of the onset of the renal failure.

SUMMARY

Renal disease is a not uncommon manifestation of progressive systemic sclerosis. Although this renal involvement may run a benign, protracted course, the more common and significant manifestation of this lesion is an acute renal failure, with relentlessly progressive oliguria and azotemia, often associated with a malignant form of hypertension. In this situation a characteristic triad of lesions is observed in the kidney: (1) intimal proliferation of the small intralobular arteries and arterioles; (2) fibrinoid necrosis involving the walls of the afferent arterioles and sometimes the glomerular loops; (3) focal cortical infarctions. The course when this acute renal lesion becomes clinically manifest is unremittently downhill. Currently available modes of therapy are not apparently effective, and may even be deleterious. Five illustrative cases, of which four were autopsied, are presented.

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SUMMARIO IN INTERLINGUA

Le occurrentia de affection del ren in sclerosis systemic progressive es cognoscite depost multe annos. In le litteratura iste complication ha recentemente recipite un attention crescente, sed il continua esser un facto frequente que illo es ignorate.

Es reportate recente experientias con iste lesion al Hospitales Peter Bent Brigham e Robert Breck Brigham. Il se tracta de cinque casos, incluse quatro in que un acute curso de oliguria, azotemia, e frequentemente hypertension progredeva rapidemente e sin remission verso le morte del subjecto. Le quinte patiente exhibiva signos

de un chronic affection renal con proteinuria e hypertension durante un periodo de quatro annos, sequite terminalmente per un phase accelerate de acute disfallimento renal. Le constatationes necroptic in quatro del patientes es presentate.

Affection renal es notate in un alte procentage del majoritate del reportate series de casos de sclerosis systemic progressive. Frequentemente iste lesion domina le tableau clinic. Le lesion renal pote sequer un benigne curso de duration prolongate, sed plus frequentemente illo seque un curso acute que se termina rapidemente in le morte del patiente. Illo pote intervenir a non importa qual puncto in le curso del morbo, e occasionalmente su occurrentia ha essite notate ante que le alterationes cutanee habeva devenite diagnostic. Le forma acute es characterisate per un declaration subitanee e un progression rapide de acute disfallimento renal con azotemia o de hypertension maligne o, plus frequentemente, de un combination del duo. Chronic affection renal es frequentemente subclinic e se manifesta usualmente in proteinuria con un sedimento urinari anormal. Ben que hypertension occurre, azotemia non es observate frequentemente. In casos rar, il se disveloppa le syndrome nephrotic. Un transition

abrupte al acute lesion renal non es incommun.

Ab le puncto de vista histologic, multe differente lesiones ha essite observate, incluse certes que on ha considerate como characteristic de altere morbos collagenicovascular. In le majoritate del casos, il ha nonobstante un predominantia del sequente triade: (1) Proliferation intimal del micre arterias e arteriolas intralobular; (2) necrosis fibrinoide afficiente le parietes del arteriolas afferente e a vices le ansas glomerular; (3) focal infarcimento cortical. Ben que iste triade es characteristic, illo non es universalmente acceptate como specific pro sclerosis systemic progressive. Omne le casos del presente reporto habeva lo, incluse le caso de un patiente normotensive. In casos chronic on trova provas de un damnification renal de longe duration, como per exemplo de hyalinisation glomerular e de fibrosis interstitial. Le prognose pro patientes con sclerosis systemic progressive e acute lesion renal es multo mal. Le superviventia probabile in le casos reportate variava inter cinque dies e septe septimanas, i.e., le superviventia medie esseva inter duo e tres septimanas. Le curso es influentiate pauco o non del toto per le currentemente disponibile modos de tractamento. Il es possibile que agentes antihypertensive effectua solmente un aggravation o precipitation del disfallimento renal. Es etiam opinate que le administration de ACTH o de corticosteroide pote inducer lesiones reno-vascular o accelerar los si illos pre-existe. Viste que tres del patientes in le presente serie disveloppava typic lesiones renal sin haber ingerite ille hormones intra al minus sex menses ante le declaration de acute disfallimento renal, le autores opina que corticosteroides non es responsabile pro omne le lesiones renal que es observate in patientes con sclerosis systemic progressive.

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A STUDY OF THE ROLE OF ACUTE INFECTIONS IN PRECIPITATING CRISES IN CHRONIC HEMOLYTIC STATES*†

By Claude-Starr Wright, M.D., F.A.C.P., and Edward Gardner, Jr., Ph.D., Augusta, Georgia

We have been impressed by the frequent coincidence of acute hemolytic crises in chronic hemolytic syndromes and the onset of acute infectious states such as the common cold. Herrick, in the first reported case of sickle cell anemia in 1910, observed: "Two days prior to examination he had 'taken cold,' his cough had grown worse and he had a slight chill, followed by fever." This association has been noted by other observers. 2, 3

To validate this clinical impression, we reviewed 23 consecutive admissions to our hospital of patients with sickle cell anemia in acute hemolytic crisis (table 1). All had hemoglobins of less than 7 gm.%. Twenty-two of the 23 had various infections, with the respiratory tract predominating, and most of these were in the acute stages or complications of coryza.

Table 1
Infections and Acute Hemolytic Crisis in Sickle Cell Anemia

Admissions for acute hemolytic crises of SCA (Hb = <7 gm. %) 23 Associated infections:

| Respiratory | 1.4 |
|-------------------------|-----|
| G. U. tract | 3 |
| Rheumatic fever | 1 |
| Pneumococcic meningitis | 1 |
| Infectious hepatitis | 1 |
| Leg ulcers | 1 |
| Gastroenteritis | 1 |

22

In an earlier study of the susceptibility of red blood cells to phagocytosis by macrophages, it was noted that individuals serving as controls, on developing acute coryza, showed a marked enhancement of phagocytosis of their red blood cells. Study of this apparent modification of the red cell surface by virus was pursued on the thesis that this additional insult is the "last straw" in persons whose bone marrow is already struggling to maintain

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effective erythroid balance. Using in vitro and in vivo virus-treated red blood cell as the model, our studies have progressed along three general lines:

- 1. Testing their susceptibility to phagocytosis by macrophages.
- 2. Determining the antigenic modification.
- 3. Determining the cell survival in rabbits and chickens, using radio-chromium (Cr⁵¹) labeled cells.

The earlier part of these studies was made in collaboration with Dr. Matthew Dodd and his associates at Ohio State University.

MATERIALS AND METHODS

Clinical Material: All patients with acute hemolytic crisis associated with sickle cell anemia who have been admitted to the Eugene Talmadge Memorial Hospital since its opening in 1956 were reviewed.

Viruses: Allantoic fluid containing Newcastle disease virus (NDV) with a hemagglutinin titer of 2048 was used. This virus was originally isolated from a chicken with a fatal case of the disease, and had been passaged many times in fertile hen eggs. Hemagglutinin titers of 512 and 1024 were obtained with the influenza virus.

Experimental Infection with NDV: Eight- to 10-week old chickens from commercial stock were injected intracardially or intravenously via wing vein with 0.2 ml. to 0.5 ml. of undiluted virus material.

Virus Hemagglutinin and Hemagglutination Inhibition Titrations: Virus hemagglutinin titrations were carried out by adding doubling dilutions of virus suspension in 0.5 ml. amounts of buffered saline and 0.5 ml. of a 0.5% suspension of human type O cells. Tubes were incubated for from one to two hours at 20 to 25° C. and read on the basis of the pattern of sedimented cells.

Hemagglutination inhibition tests were carried out by preparing double dilutions of serum in 0.25 ml. of buffered saline and adding four hemagglutinating units of virus contained in 0.25 ml. and 0.5 ml. of a 0.5% suspension of erythrocytes to each serum dilution. Incubation and reading of tests were the same as described above.

Erythrocyte Survival: Rabbit and chicken erythrocytes were tagged with radiochromium (Cr⁵¹) by the addition of 100 to 150 μ c. to whole blood in special ACD solution (Abbott). The mixture was incubated for one hour at room temperature, followed by the addition of 100 μ gm. ascorbic acid. The blood-ACD mixture was subsequently injected via wing vein, either as whole blood or as packed cells, after removal of supernatant following centrifugation.

Calculation of per cent survival was made on the basis of hematocrit values obtained at each sampling. Blood aliquots were counted using a low background, well-type scintillation counter.

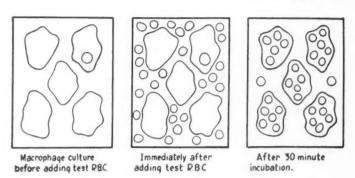


Fig. 1. The three phases in determination of the phagocytic index. The macrophage and surrounding medium are controlled. The variable is the erythrocyte and its susceptibility to ingestion by the macrophage.

RESULTS

Phagocytosis of Virus-Modified Erythrocytes: A means of testing the susceptibility of erythrocytes to destruction by macrophages grown in tissue culture from rabbit spleens has been described, and is only briefed in this presentation. The unit of measuring the red cell susceptibility is the phagocytic index (designated as PI), and is determined as follows:

Three- to five-day-old cultures of rabbit spleens were observed before the addition of the test cells, diagrammed in the first panel of figure 1. The number of cells and their viability varied in a large series of such cultures; however, satisfactory cultures were obtained in from 75 to 90% of those attempted.

Since some of these macrophages already contained easily identifiable erythrocytes from the rabbit from which they were obtained, the number of these present in a total of 50 macrophages served as a base line to be subtracted from the count obtained after the addition of the test cells (figure 1, panel 2). When a suitable base line count had been made, the fluid of the

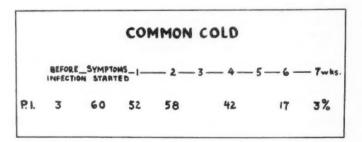


Fig. 2. The phagocytic index at weekly intervals, before, during and after acute coryza.

culture was removed and fresh fluid added along with the test erythrocytes. The cultures were replaced in the incubator and removed only for counting. A total of 50 macrophages per culture was inspected for the number of macrophages containing red cells. The base line counts were subtracted and the results finally expressed as the percentage of macrophages showing phagocytosis of the test cells (figure 1, panel 3).*

Application of the test to normal rabbit and human red blood cells revealed a phagocytic index (PI) of less than 12%, with an average of 5.4% for normal human cells. Elevated phagocytic indices have been noted in red blood cells from patients with most clinical hemolytic syndromes, ma-

lignant diseases and many infectious diseases.

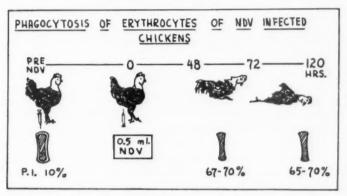


Fig. 3. The elevated phagocytic index (PI) of chicken erythrocytes during the course of induced Newcastle disease is interpreted as reflecting in vivo modification of the red cell.

In vitro modification of erythrocytes, such as cells sensitized with specific isohemagglutinin and heterohemagglutinin, trypsin-treated cells and cells treated with virus, has always resulted in increased susceptibility to phagocytosis. The latter modification, i.e., virus-treated cells, is developed in this presentation.

As previously mentioned, we noticed that there was a marked elevation of the *phagocytic index* during the symptoms of the common cold. The elevation occurred early, frequently in the first few hours of symptoms, and did not return to normal until from four to seven weeks later. Figure 2 summarizes these findings in a typical case where the PI before symptoms was 3%, rose to 60% the first day, and in the following weeks was 52, 58, 42, 17, and finally returned to the "pre-cold" level of 3% after seven weeks. This type of elevation in coryza has been repeatedly observed.

The first part of this study dealt with determination of the *phagocytic* index of in vivo and in vitro virus-treated red blood cells. Testing the sus-

^{*} Time lapse motion pictures were used to illustrate the microscopic observations.

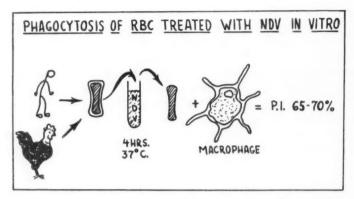


Fig. 4. Both human and chicken red cells treated with Newcastle disease virus in vitro are more susceptible to macrophage ingestion thus resulting in a high phagocytic index.

ceptibility to phagocytosis of erythrocytes of Newcastle disease virus-infected chickens was carried out in the following manner:

Four- to six-week-old chickens which were highly susceptible to Newcastle disease were inoculated in the heart with 0.5 ml. of a suspension of NDV of high titer. The chickens began to come down in from 48 to 72 hours with the usual symptoms of the disease, resulting in prostration and death 72 to 120 hours after inoculation (figure 3). It was noted that from the onset of symptoms the PI was elevated to 65 to 70%. Elevated PI's were detected as early as four hours after inoculation in many instances.⁵

For the sake of simplicity, we have depicted the normal red blood cell in figures 4 and 5 as having an outer coating, and the virus treated or "modified" cell without this overcoat.

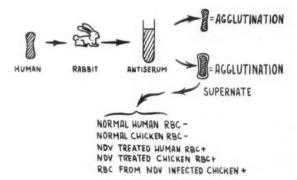


Fig. 5. Antigenic specificity of virus modified erythrocytes is demonstrated by injection of Newcastle disease virus treated human cells into the rabbit with the development of an antiserum, which after absorption, agglutinated NDV treated human and chicken erythrocytes but not untreated cells.

Testing the susceptibility to phagocytosis of erythrocytes treated with Newcastle disease virus in vitro was carried out as follows: Human and chicken red cells were added separately to undiluted NDV and incubated at 37° C. for four hours. The treated cells were then washed four times and tested in the culture of macrophages. The resulting "modified" red blood cells had indices in the same range as the in vivo treated cells (figure 4).6

Antigenic Specificity of Virus-Modified Erythrocytes: Antigenic studies were carried out as follows: Human type O red blood cells were treated with virus as described. These cells were then employed as antigen in the immunization of rabbits. The resulting antiserum agglutinated virus-treated red blood cells as well as normal red cells (figure 5). Subsequent absorp-

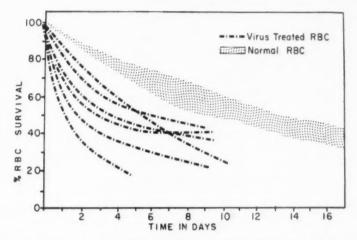


Fig. 6. The survival of in vitro virus (influenza) treated red blood cells in six rabbits is compared with a controlled group of 20 normal red cell survivals (shaded area).

tions with normal erythrocytes, as indicated by the lower series of arrows, completely removed the normal cell antibody and allowed the isolation of hemagglutinin which specifically agglutinated virus-modified erythrocytes. In the lower tabulation, it is noted that the absorbed serum fractions did not agglutinate normal human and chicken red blood cells, but did agglutinate in vitro virus-treated human and chicken red cells as well as in vivo virus-treated chicken erythrocytes.⁷

The Effect of Viruses on the Survival of Erythrocytes: This was studied by two methods: (1) erythrocytes were exposed to the action of virus in vitro and subsequently tagged with radiochromium (Cr⁵¹), reinjected, and the course of the survival was followed in rabbits; and (2) the survival of the red blood cells was determined in chickens after induced infection with NDV.

Figure 6 shows the survival of in vitro (NDV) virus-treated red cells compared with the survival of normal untreated cells in normal rabbits (shaded area). It is evident that a significant shortening of the life span of the treated cells occurred.8

Figure 7 indicates the shortened survival of erythrocytes in two of three chickens infected by the injection of Newcastle disease virus.* The normal range is indicated again by the shaded area. The normal 50% apparent survival time in these animals was nine to 11 days. The 50% survival time in two of the animals infected with virus was four and one-half to six and one-half days. The third animal similarly exposed proved to be highly resistant to infection, and demonstrated no shortening in survival time.*

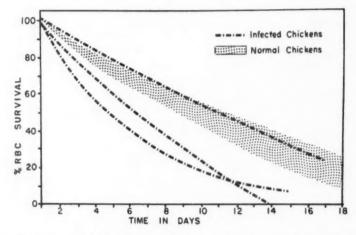


Fig. 7. The shortened survival of red blood cells during the course of Newcastle disease is interpreted as reflecting in vivo modification of the cells. The third animal proved to be highly resistant to infection and demonstrated no shortening in red cell survival time.

CONCLUSION

These data—i.e., that the virus-treated red blood cell (1) is more readily phagocytized than the normal red blood cell; (2) is antigenically different from the normal red blood cell, and (3) has a shortened in vivo life span—suggest that virus modification of red blood cells may trigger an acute hemolytic crisis in chronic hemolytic states. Clinical observations substantiate this concept. Twenty-two of 23 consecutive admissions of patients with sickle cell anemia in acute hemolytic crisis had various infections, with the respiratory tract predominating. Most were in acute stages or complications of coryza.

^{*}Animals from commercial stock had been vaccinated against Newcastle disease and exhibited varying resistance to induced infection.

SUMMARIO IN INTERLINGUA

Nos ha essite impressionate per le frequente coincidentia de acute crises hemolytic in chronic syndromes hemolytic e le declaration de statos infectiose acute, como per exemplo le rheuma commun. Pro validar iste impression clinic, nos ha revistate le casos de 23 patientes admittite consecutivemente a nostre hospital con anemia a cellulas falciforme in acute crises hemolytic. Vinti-duo del 23 habeva varie infectiones, con predominantia del vias respiratori, e in le majoritate de iste casos il se

tractava del stadios acute de complicationes de coryza.

In un previe studio concernente le susceptibilitate de erythrocytos al activitate phagocytotic de macrophagos, il esseva notate que individuos in le gruppo de controlo manifestava post le disveloppamento de corvza un marcate intensification del phagocytosis de lor erythrocytos. Le studio de iste apparente modification del superficie erythrocytic per le activitate de virus esseva continuate super le base del these que le insulto additional del virus representa le "colpo de gratia" in subjectos in qui le medulla ossee es jam ingagiate in un lucta desperate pro mantener un efficace balancia erythroide. Varie investigationes-omnes laborante con le principio del exposition de erythrocytos al effecto de virus-ha resultate in le sequente observationes: (1) Erythrocytos tractate in vitro o in vivo con virus de Newcastle, de parotiditis, e de influenza esseva phagocytisate plus prestemente per macrophagos histocultural que normal cellulas de controlo. (2) Le tractamento de erythrocytos in vitro o in vivo con virus de Newcastle, de parotiditis, e de influenza modificava le antigenicitate de erythrocytos in comparation con lor comportamento normal. (3) Erythrocytos tractate in vitro con virus de influenza habeva un reducite longevitate in conilios secundo mesurationes effectuate per medio del marcation de cellulas con chromo radioactive (Cr51). Le reducite longevitate de erythrocytos durante le curso de morbo de Newcastle es interpretate como effecto del modification del cellulas in vivo.

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ALARMING NEUROMUSCULAR REACTIONS DUE TO PROCHLORPERAZINE * †

By Janis Gailitis, M.D., Richard R. Knowles, M.D., and Arturo Longobardi, M.D., Newbort, Rhode Island

PECULIAR aneuromuscular reactions of the dystonic type have been reported as infrequent side-effects of prochlorperazine therapy.1 This socalled extrapyramidal syndrome presents a frightening experience to the patient and a diagnostic challenge for the physician. Four such episodes were observed in Newport Hospital in the years 1958-1959.

CASE REPORTS

Case 1. A 25 year old white female was admitted on April 19, 1958, with low abdominal pain, fever and vomiting. She had been discharged 12 days previously after a dilatation and curettage for diagnostic purposes. A tentative diagnosis of pelvic inflammatory disease was made, and treatment with parenteral penicillin and streptomycin was begun. Prochlorperazine was administered to alleviate vomiting and restlessness.

On April 21, two hours after the last dose of the drug, the patient's eves suddenly rolled upward in a fixed gaze, her head turned to the left, and her neck became hyperextended and her arms rigid. She was fully oriented but frightened, and cried out for help. The attack lasted about four minutes. A similar episode occurred a few hours later. During these attacks there was impairment of swallowing and speech, with the patient able to produce only gasping and grunting sounds. After amobarbital sodium (0.25 gm.) was administered intravenously no further attacks occurred, and the patient was discharged two days later, asymptomatic except for mild restlessness and some stiffness of the neck and extremities.

Comment: The diagnosis in this case was made in retrospect 15 months later, after the patient's physician had become familiar with these reactions and had seen case 4. His first impression was that she had had a hysterical attack. The possibilities of catatonic schizophrenia and tetanus were also entertained. The dosage of prochlorperazine (80 mg. over the three-day period) was not high. The patient responded rapidly to sedation with amobarbital sodium and discontinuance of prochlorperazine.

Case 2. A 33 year old housewife was admitted on February 1, 1959, complaining of dizziness, nausea, vomiting and "buzzing" in her right ear. A diagnosis of Menière's syndrome was made, and treatment with intravenous fluids and prochlorperazine was begun.

On this regimen the patient gradually improved, and when examined on February 3, at 9 a.m., her only complaints were pain and tightening of her neck and face. Two

^{*} Received for publication November 6, 1959. From Newport Hospital, Newport, Rhode Island.

[†] Available as Compazine from Smith, Kline and French Laboratories, Philadelphia. Requests for reprints should be addressed to Richard R. Knowles, M.D., 230 Bellevue Avenue, Newport, Rhode Island.

hours later she suddenly developed hyperextension of the neck and distortion of her face, with involuntary protrusion of the tongue. When examined 10 minutes later the most remarkable findings were opisthotonos and grotesque contortion of the face, with the lips puckered and the tongue protruded. Her mouth was drawn to the right and her eyes were fixed in an upward gaze. Marked cyanosis and hyperactive tendon reflexes were noted. The patient was fully oriented, but frightened. Her speech was thick, and she had difficulty in swallowing. The remainder of the physical examination was within the normal range.

At first this episode was thought to represent a hysterical reaction, but the possibilities of a cerebral vascular accident or tetanus were suggested by a consultant. The correct diagnosis was made about two hours later after a search of the literature on the side-effects of prochlorperazine therapy. The reaction lasted about one hour, and subsided after an intramuscular injection of amobarbital sodium (0.25 gm.). A similar attack, lasting 30 minutes, occurred four hours later; again, prompt relief followed an injection of amobarbital sodium. The next day, except for fear of another attack, the patient was fully recovered, and she remained asymptomatic until

discharge.

Comment: This patient developed an alarming neuromuscular reaction after 90 mg. of prochlorperazine, administered over a period of two days. The episode was in every respect similar to those reported in the literature. The premonitory symptoms of muscle tightness and pain were not properly evaluated. The dosage might have been too high, especially when the patient's dehydration and low urine output are considered. The time interval of 28 hours between the last dose of prochlorperazine and the onset of the reaction may be explained by the slow release of the drug from a long-acting spansule. Some respiratory embarrassment was present, as evidenced by cyanosis. For the patient and her physician, it was a distressing experience.

Case 3. A 22 year old graduate nurse was admitted on May 13, 1959, with acute appendicitis. She was operated upon a few hours after admission and an acutely inflamed appendix was removed. During the immediate postoperative period,

prochlorperazine was administered to lessen nausea.

On the third postoperative day, 25 mg. of prochlorperazine were given intramuscularly because of severe vomiting. The next day the patient complained of spasm in her throat, protrusion and thickness of the tongue, and inability to focus her eyes. On examination, her mouth was pulled to one side and the teeth were clenched. The reaction subsided within 20 minutes after an injection of meperidine and atropine. Later that day the patient again developed twitching of the upper lip, turning of the eyes to the right, gradual opening of the mouth, protrusion of the tongue and marked cyanosis. She was fully oriented, but frightened. These episodes recurred three times, lasting from a few seconds to 30 minutes. They subsided each time after the administration of meperidine and atropine. The next day the patient was tense, restless and afraid to sleep, but no further dystonic episodes occurred, and she was discharged asymptomatic two days later.

Comment: A severe dystonic reaction developed after 40 mg. of prochlorperazine over a period of four days. The dose of 25 mg. given intramuscularly on May 17 appears to have been excessive. The diagnosis was made by the floor nurse who had had experience with case 2. The patient's

physician was unfamiliar with such reactions from prochlorperazine. Considerable cyanosis during the attacks indicated respiratory distress. Treatment with meperidine and atropine was apparently effective.

Case 4. A 43 year old Negro female was admitted on July 23, 1959, with the complaints of involuntary movements of her face, tongue and neck. Two days before she had been advised to take prochlorperazine, 5 mg. every four hours, for nausea and an upset stomach. The next day she began to experience involuntary protrusion of her tongue and retraction of her mouth. The attacks lasted only a few minutes, but recurred several times. In an attempt to control these symptoms, the dose of prochlorperazine was doubled and the patient fell asleep.

On awakening the following morning her eyes were rolled upward and her tongue and face were contracted on the right side. She was fully oriented. The symptoms were felt to represent a reaction to prochlorperazine, and the attacks subsided shortly after the administration of phenobarbital sodium (130 mg. intramuscularly). The hospital course was uneventful, and the patient was discharged a few

days later.

Comment: A dystonic neuromuscular reaction developed after a moderate dose of prochlorperazine in a middle aged, hypertensive patient. The initial symptoms were not recognized, and the patient was advised over the telephone by her physician to double the dose of the drug. Consequently, she suffered a rather severe attack requiring hospitalization. The diagnosis was made by a consultant. After prochlorperazine was withdrawn, the patient recovered.

DISCUSSION

Prochlorperazine has been widely used as an effective antiemetic and ataractic agent. Although this drug is a halogenated phenothiazine derivative, serious side-effects have been infrequent. In 1957, reports began to appear in the European literature describing an acute dyskinetic neuromuscular syndrome in patients treated with large doses of prochlorperazine. Later, in this country, O'Hara ³ and Christian and Paulson ⁴ published similar observations. Similar reactions have also been noted in patients treated with perphenazine, another halogenated phenothiazine. ^{5, 6}

As our cases illustrate, the acute motility disturbance induced by prochlorperazine may be quite alarming and potentially dangerous. Marked cyanosis due to respiratory distress occurred in two cases. In O'Hara's series, two patients dislocated their jaws. If these reactions are not promptly recognized, serious diagnostic and therapeutic errors are possible. The psychologic impact of these episodes should not be minimized. All of our patients were extremely fearful of a recurrence of their attacks. Although these reactions are usually associated with high dosage of the drug (over 60 mg. per day), our experience indicates that they may be induced with small or moderate doses early in the course of the treatment.

The time element seems to be important. The reactions occurred within one to three days after institution of therapy. Twice we observed the con-

TABLE 1

| | | Т | ABLE 1 | | |
|----------------|--------|------------------------------|-----------------------------|--|--|
| Date | Dose | Route | Total Dose in 24 hrs. | Time of Administration | Remarks |
| | | Dosage of Proch | lorperazi | ne in Case 1 | |
| April 19, 1958 | 10 mg. | By mouth and intramuscularly | 20 mg. | 4:30 p.m. and 9 p.m. | |
| April 20, 1958 | 10 mg. | By mouth | 40 mg. | 8–12 a.m. 4–8 p.m. | |
| April 21, 1958 | 10 mg. | By mouth | 20 mg. | 8–12 a.m. | Reaction to prochlor- perazine at 2 p.m. |
| | | Dosage of Proch | lorperazi | ne in Case 2 | |
| Feb. 1, 1959 | 30 mg. | By mouth (spansule) | 60 mg. | 2 p.m. and 10 p.m. | |
| Feb. 2, 1959 | 30 mg. | By mouth | 30 mg. | 6:45 a.m. | |
| Feb. 3, 1959 | - | (spansule) — | _ | | Reaction to prochlor- perazine at 10:45 a.m. |
| | | Dosage of Proch | lorperazi | ne in Case 3 | |
| May 14, 1959 | 5 mg. | By mouth | 5 mg. | 6:30 p.m. | |
| May 15, 1959 | 5 mg. | By mouth | 5 mg. | 10:30 a.m. | |
| May 16, 1959 | 5 mg. | By mouth | 5 mg. | 9 a.m. | |
| May 17, 1959 | 25 mg. | Intramuscularly | 25 mg. | 10 a.m. | |
| May 18, 1959 | - | | | - | Reaction to prochlor- perazine at noon |
| | | Dosage of Proch | lorperazir | ne in Case 4 | |
| July 21, 1959 | 5 mg. | By mouth | 20 mg. | 10 a.m. 2 p.m. 6 p.m. 10 p.m. | |
| July 22, 1959 | 10 mg. | By mouth | 40 mg. | 10 a.m. 2 p.m. 6 p.m. 10 p.m. | Reaction to prochlor- perazine at 1 p.m. |
| July 23, 1959 | - | - | - | _ | Reaction to prochlor- perazine |

siderable interval of 24 hours or more between the last dose of the drug and the onset of the attack. The reactions were strikingly similar, with a bizarre sequence of motor abnormalities. The patients were always fully oriented, but frightened. Eye movements suggestive of oculogyric crises were noted,

and grotesque distortion of the face, trismus, a protruding tongue, opisthotonos, and extensor rigidity of the extremities occurred. Difficulty in swallowing and impairment of speech were prominent manifestations. The length of such an attack varied from a few seconds to one hour.

Although the onset seemed sudden, tightening and pain in the neck and facial muscles, together with "thick" speech, preceded the attack in one case for at least three hours. The importance of these complaints as premonitory symptoms of an impending reaction was recognized only in retrospect. The development of such symptoms should be watched for closely in patients receiving prochlorperazine. If they are noted, the drug should be omitted or the dosage reduced. The differential diagnostic possibilities considered included hysterical reaction, catatonic schizophrenia, cerebrovascular accident, tetanus and strychnine poisoning.

Although the drug probably acts by suppressing inhibitory impulses from the cerebral cortex to the basal ganglia, the exact mechanism responsible for these reactions is unknown. All of these episodes were promptly controlled with sedation. In our experience, amobarbital sodium given intravenously or intramuscularly appeared to be satisfactory. Drugs used in the treatment of Parkinson's disease have been recommended, but their action seems to be too slow. Administration of caffeine has also been suggested. The prognosis appears to be good, with no ill effects persisting after recovery from these reactions.

SUMMARY

Four cases of dyskinetic neuromuscular reactions induced by prochlorperazine are reported. The clinical manifestations, differential diagnosis and treatment are described.

SUMMARIO IN INTERLINGUA

Dyscinetic reactiones neuromuscular es infrequente effectos lateral de therapia a prochlorperazina. Es describite quatro casos con manifestationes de symptomas extrapyramidal post le administration de prochlorperazina. Omne iste patientes exhibiva un alarmante serie de anormalitates motori, con irreprimibile movimentos ocular que suggereva crises oculogyric e con grottesc distorsiones facial, protrusion del lingua, trismo, e rigiditate extensori. Nulle del patientes se trovava disorientate, sed omnes esseva terrificate e habeva grande difficultates de inglutition e de parolar. In un del patientes iste symptomas esseva precedite de tensitate del musculos del collo e de "spissification" del parolar. Le possibilitates de diagnose differential suggerite per le tableau clinic includeva hysteria, schizophrenia catatonic, tetano, invenenamento strychninic, e un accidente cerebro-vascular.

Le reactiones occurreva intra un a tres dies post le institution del therapia a prochlorperazina e post un dosage total del droga de inter 40 e 90 mg. In duo casos le reactiones non se faceva manifeste usque a plus que 24 horas post le administration del ultime dose.

Le pathogenese de iste reactiones non es cognoscite. Le interruption del medication e simple mesuras de sedation resultava in le prompte disparition del symptomas. Il habeva nulle sequellas.

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UNILATERAL RENAL DISEASE AS A CAUSE OF HYPERTENSION: ITS DETECTION BY URETERAL CATHETERIZATION STUDIES * †

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It has been amply demonstrated experimentally that renal ischemia can result in hypertension 1-3 and that, in man, reduced arterial flow to one kidney may produce a clinical picture indistinguishable at the bedside from so-called "essential" hypertension. 4-7 Following Butler's initial observations in 1937 of the relief of hypertension in a child after the removal of a diseased kidney,8 many reports appeared on the results of nephrectomy for hypertension. Up to 1954 the percentage of "cures" in any sizable series of cases was remarkably low, and rarely did more than 20% of operations provide the desired fall in blood pressure.9-11

The search continues for methods whereby disease in one kidney may be identified as causative (or noncausative) in a patient with hypertension—first, to provide cure to the moiety of hypertensive subjects who are susceptible to surgical intervention, and second, to avoid needless operations on patients to whom no benefit would accrue.

In 1954, and again in 1957, the authors reported observations on simultaneously collected urines from both kidneys in hypertensive subjects for the purpose of identifying unilateral renal ischemia which was inducing hypertension. 5, 12 The studies were prompted by two series of observations. Berthrong 5 had provided convincing anatomic evidence of renal ischemia in sizable segments of renal parenchyma in those kidneys which had been removed with relief of hypertension, and White 13 has demonstrated in animal experiments that partial constriction of one renal artery

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resulted in a marked reduction in urine flow, with lower sodium concentration from the ischemic kidney. In similar experiments, Berliner and Davidson 14 have provided further convincing evidence that reduced urine volume and lower sodium concentrations are characteristic manifestations of reduced renal arterial flow.

Our earlier observations with ureteral catheterization studies in hypertensive subjects were uniformly in keeping with such a thesis.^{5, 12} In the present communication the authors report further experience with this method of identifying unilateral renal ischemia which may be causing hypertension. Our current procedure in evaluating these patients is presented, along with a discussion of some of the problems in the interpretation of the results.

METHOD

A detailed outline for the proper performance of ureteral catheterization studies has been recorded in a previous report by the authors.¹² Therefore, only a brief summary of the procedure will be recorded here.

1. Diets of normal sodium content were given to the patients during a four- to five-day period preceding the study. All diuretics were discontinued. If the patient had been taking chlorthiazide, sodium repletion was begun seven to 10 days before the catheterization study. These steps were necessary to avoid unusually low sodium concentrations in the urine of patients who had been subjected to prolonged periods

of sodium depletion.

2. The patients were given 800 c.c. of tap water orally during the hour preceding cystoscopy; catheters were then inserted into the ureters to a distance 1 to 2 cm. above the ureteropelvic junction.* When urine flow was adequate (1 to 3 ml./minute from the "better" kidney), a third catheter was inserted into the bladder to determine the amount of leakage around the ureteral catheters, and the simultaneous collections were begun. As soon as 30 to 50 ml. of urine were obtained from one kidney, the containers were removed and another collection period was begun.

 The volumes of urine were measured in graduated cylinders, and sodium determinations were performed on each specimen.¹⁵

4. Additional precautions observed during the study:

a. Constant observation of urine flow.

- b. Proper hydration of patient, using oral route; if intravenous route was required, solutions containing sodium were not used, except as noted in table 1.
- c. Two or three collection periods preferred, obtaining 30 ml. or more urine from one kidney during each period.
- d. Bladder emptied at end of each collection period.
- 5. The results were discarded and the test was repeated when any of the following occurred:
 - a. Cessation of urine flow during a collection period.
 - b. Excessive leakage of urine around the ureteral catheters.
 - c. Urine sodium concentration less than 10 mEq./L. from each kidney.

^{*}The authors wish to acknowledge the expert assistance of our urologic colleagues who carried out the ureteral catheterizations. We are particularly indebted to the urologists at the Brady Institute and the Department of Gynecology of The Johns Hopkins Hospital, and the Departments of Urology at the University of Maryland and Baltimore City Hospitals.

Table 1—Ureteral Catheterization Studies on Patients Benefited by Nephrectomy

| | | | | | Urir | ie | | | Renal | Follow-up | | |
|-------------|--------------------|--------------------|---------------------------|----------------------------|-------------------|-------------------|-------------------|------------------|-------------------|--|---|--|
| Case No. | Patient Age-Sex | Pressure PreOp. | Vo | lume ml | | Sodium mEq./L. | | Arterio- gram | Blood Pressure | | | |
| | | rieop. | Left | R | ight | Left | Ri | ight | | | | |
| | | | | | | | | | | 6 years | | |
| 1 | I. N. (37-M) | 200-240 110-140 | 100 10 | | 10 | 19.0 11.7 | | 1.7 | + | 140-150 80-95 | | |
| 2 | R. M. (50-M) | 200-220 100-120 | 22 | 53 5 | | 22 9 | | 117.4 | 9 | 9.2 | + | 3 years 140–160 75–90 hypertension recurred in 4th year |
| 3 | S. B. (61-M) | 220-270 130-150 | 53 | | | 19.4 | | 12.8 | not done | 15 months 170-200 90-100 (died CVA) | | |
| | | | 50 | | 13 | 48.0 | 4 | 0.0 | | 3 years | | |
| 4 | N. T. (20-F) | 180-240 | 50 | | 4 | 43.0 | | 24.0 | not done | 120-130 | | |
| 4 | (20-1) | 110-140 | | | 8 | 119 | | 06 | | 70-80 | | |
| | - | | *61 | olume m | 1 | - | ım mEq | | | | | |
| | | | L R | | В | L | R | В | | | | |
| | | | 14 | 4 | 0 | 69 | 56 | - | | 2 years | | |
| 5 | J. T. (14-M) | 150-210 110-140 | 3.2 9.0 25 | 1.7 2.6 14 | 0 0 0 | 62 114 22 | 34 33 12 | | + | 130-140 60-80 | | |
| | | | 7 | 13 | 3 | 57 | 126 | | | 16 months | | |
| 6 | G. S. (8½-M) | 175-230 120-160 | 7.5 †5.6 †7 †7.6 | 17.5 13.8 10.4 13 | 2.4 1.9 6.4 | 104 118 123 | 115 142 137 | | + | 110-126 70-80 | | |
| | | - | 5 | 27 | 0 | 61 | 121 | | | 12 months | | |
| _ | W. M. | 160-210 | 8 | 37 | 4 | 37 | 91 | | + | 120 | | |
| 7 | (40-M) | 100-120 | 22 21 | 49 52 | 188 210 | 13 8 | 73 39 | 47 33 | , | 80 | | |
| | | | | | | | | | | 7 months | | |
| 8 | M. B. (40-F) | 200-220 120-140 | 5 7 | 59 84 | 33 53 | 3 4 | 25 27 | 26 30 | + | ‡ <u>140</u> 90 | | |
| 6 | L. G. | 170-220 | 52 51 | 24 22 | 0 | 29 29 | 12 12 | | + | 6 months | | |
| 9 | (27-F) | 110-140 | 74 76 68 | 32 31 27 | 0 0 | 18 25 29 | 4 5 7 | | | 70 | | |

* I.V. NaCl infusion during test. † Received I.V. sodium PAH during these 3 periods. ‡ Renal endarterectomy performed.

d. Urine volume inadequate (less than 1 to 2 ml. urine from one kidney).

e. Results not consistent in all collection periods.

f. Excessive blood in small volumes of urine (5 to 10 ml.).

Even though the strictest care was exercised, the authors admit that from 15 to 20% of the catheterization studies were noninterpretable for one or another of the technical reasons mentioned. Repeating the test at a later date, however, was frequently rewarding.

RESULTS

Using this technic, the authors have studied 210 hypertensive subjects. Fifty-eight patients were considered to have "essential" hypertension by currently accepted criteria. The results in this group revealed urine volumes and sodium concentrations nearly identical from each kidney, as previously reported.12 In several instances where a difference in the excretion from the two kidneys was observed, there was never more than a

EXPLANATION OF TABLE 1

Interpreting the data in this table requires some explanation.

Ureteral Catheterization Studies: The urine volume and sodium measurements obtained simultaneously from each kidney are recorded. The letters L, R, B at the lower half of the

table refer to left ureter, right ureter and bladder, respectively.

*Renal Arteriogram: Arteriography was performed in seven patients. A plus sign indicates that a constriction or absence of the main renal artery was demonstrated in the kidney that was secreting the lesser urine volume with lower sodium concentration. In the two patients (cases 2 and 6) in whom no main renal artery was visualized, three or four small arteries arising from the aorta were seen supplying this kidney, and there was a lesser concentration of dye throughout the renal parenchyma.

Surgical Procedure: In each patient with the exception of case 8, the kidney that secreted

less urine with lower sodium concentration was removed. In case 8, renal endarterectomy was

performed and the kidney was not otherwise disturbed.

Complete clinical details on cases 1, 2, 3 and 4 have been reported previously.

**Case 4 (N. T.): The studies on this patient seem worthy of reemphasis. This subject had the catheter study performed on three different occasions, with consistent results. During the third study the patient was given an intravenous infusion of 0.9% sodium chloride, and it will be noted that the differences in sodium concentration secreted by the two kidneys were less

striking than during the previous two studies, when hydration with water alone was used.

Case 5 (J. T.): The patient had the test performed on two occasions, always with consistent

lowering of urine volume and sodium concentration on the right side.

The broken line indi-Case δ (G. S.): All the collections were made at a single cystoscopy. cates the beginning of the infusion of sodium para-aminohippurate. (The renal clearance studies were performed by Dr. David Grob, Department of Medicine, the Johns Hopkins Hospital.) It will be noted that urine volume and sodium concentrations were consistently reduced in all collection periods on the left side; but during the period of sodium PAH infusion, the differences in sodium concentration from the two kidneys were much less impressive.

Case 7 (W. M.): This patient had two separate catheter studies, repeated three months In the second study there was excessive leakage around the ureteral catheters, resulting in a large volume of bladder urine. The sodium concentration of the bladder urine nearly paralleled the sodium concentration in the urine from the right ureter, indicating that most of the urine in the bladder came from the right kidney. (The authors wish to emphasize that attempts to identify the source of bladder urine by comparing urine sodium concentrations may be subject to error. However, in this instance, and in case 8, where there was such a marked difference in sodium concentration from each kidney, and nearly an identical amount of sodium in the urine from the bladder and right ureter, it seemed reasonable to assume that most of the bladder urine had been derived from the right ureter.)

Case 8 (M. B.): Excessive leakage around the ureteral catheters made volume measurements questionable until one examined the urine sodium concentrations; these indicated that

the source of the bladder urine was undoubtedly from the right side.

Case 9 (L. G.): This patient had the study performed on two occasions, three months apart, always with consistent reduction of urine volume and sodium concentration from the right kidney. This patient was of special interest in that she was known to have had hypertension for seven years—the greatest duration of hypertension of any patient in this group.

TABLE 2 Patients Subjected to Nephrectomy without Effect on Hypertension

| | | | Blood Pressure PreOp. | | | | | | | |
|-------------|--------------------|--|-----------------------------|-----------------|----------------|--------------|--------------------|----------------|----------------|---------------------------------|
| Case No. | Patient Age-Sex | Diagnosis Pre-Op. | | 1 | olume. | ml. | Sodium mEq./L. | | | Follow-up Blood Pressure |
| | | | L | R | В | L | R | В | | |
| 1 | V. H. 57-M | Tumor, left kidney? | 195-240 105-140 | 35 | 55 | 0 | 5.1 | 3.7 | 0 | 11 months 195 110 |
| 2 | P. W. 18-F | Hypoplasia left kidney† | 140-165 95-110 | 6 | 46 | 10 | 24 | 21 | 25 | 17 months |
| | | , | 93-110 | 12 | 23 | 104 | 16 | 17 | 16 | 95-105 |
| 3 | B. H. 41-F | Hypoplasia right kidney | 170–180 105–120 | 38 | 6 | 0 | 19 | 26 | 0 | 12 months 150–170 105–115 |
| 4 | L. B. 9-F | Pyelonephritis, right† | 150-180 110-130 | 45 28 45 | 18 15 | 36 61 | 20 14 41 | 22 16 | 13 10 42 | 6 months 150–170 110–130 |
| | | | | 35 | 4 | 26 | 41 | 41 | 41 | 110 100 |
| 5 | I. W. 58-F | Pyelonephritis, right | 160-195 80-95 | 43 43 138 | 2 6 9 | 0 0 0 | 29 24 35 | 25 23 33 | | 15 months 150-210 75-110 |
| 6 | O. G. 55-M | Pyelonephritis with stone, right | 180-210 100-120 | 40 | 13 | 0 | 11 | 21 | | 18 months 180–200 110–120 |
| 7 | E. B. 56-F‡ | Stenosis, left renal Artery | 220-240 125-160 | 29 | 32* 28 | 1 | 61 | 63 63 | 15 | 12 months 200-240 |
| | | Arteriogram | | 27 | 25 31 | 3 | 70 | 77 70 | 4 | 120-140 |
| 8 | L. R. 37-F‡ | Small left renal artery with poor Arborization Arteriogram | 180-220 110-140 | 37 7 7 | 46 12 10 | 0 0 | 23 | 19 | 9 | 12 months 220-210 120-140 |

* Two ureters from right kidney.

† Renal arteriogram revealed smaller main renal artery on affected side with no obstruction to blood flow.

‡ I¹³¹ Diodrast renograms indicated decreased arterial flow in left kidney.

EXPLANATION OF TABLE 2

This table presents the data in essentially the same fashion as does table 1. Each of these patients presented with hypertension and an abnormality in one kidney by intravenous pyelogram and/or renal arteriogram. In each instance the "abnormal" kidney was smaller and secreted less urine than did its companion; the "abnormal" kidney was surgically excised.

The clinical and catheterization data on cases 1, 2, 3 and 4 have been reported previously.
The authors are indebted to Dr. T. E. Woodward, Dr. John D. Young and Dr. S. T. Revell for

TABLE 3 Ureteral Catheterization Studies M. H. (37-F) B. P. $\frac{180-220}{110-120}$

| | Per | iod I | Peri | od II bo | Period III | | |
|----------------------------------|----------|----------|----------|----------|------------|------------|--|
| | Left | Right | Left | Right | Left | Right | |
| Volume (ml.) Sodium (mEq./L.) | 49 83 | 34 76 | 57 29 | 45 18 | 67 16.7 | 54 13.5 | |

Aortogram-? Decreased vascularity, lower pole, right kidney. No benefit from right nephrectomy.

20% reduction in urine volume from one kidney, and sodium concentrations never differed by more than 5% in any one patient.

All patients who demonstrated at least a 50% reduction in urine volume from one kidney, and a 15% or more reduction in sodium concentration on this same side, obtained striking relief of hypertension following surgical procedures (table 1). In each instance there was anatomic evidence of a reduction in arterial blood supply to nearly the entire kidney that was inducing hypertension.

Equally significant, perhaps, are the studies on eight other patients with radiographic evidence of unilateral renal disease, in whom the catheterization study disclosed a lowering of urine volume from the "diseased" kidney, but sodium concentrations were equal or greater from the side with the lesser volume—a pattern distinctly different from that of the preceding group. In these latter eight patients, nephrectomy was followed by no significant alteration in blood pressure (table 2).

Another patient was subjected to nephrectomy whose catheter study disclosed 20 to 30% less urine from one side, and 10 to 30% lower sodium concentration in that same urine (table 3). No improvement in the hypertension followed removal of this kidney, which showed only mild arteriosclerosis on histologic examination.

permission to report the studies on cases 7 and 8. More complete clinical details on these patients will be published in a separate report.

Case 5 (I. W.): The results in the first collection period were equivocal, with lower urine volume and slightly lower sodium concentration on the right side. However, subsequent collection periods revealed no significant difference in sodium concentration from the two kidneys. This case emphasizes the value of multiple collection periods in the study.

Case 6 (O. G.): Interpreted as a "negative" test because of the higher sodium concentration from the kidney that was secreting the lower volume.

Case 7 (E. B.): This patient had a double collecting system on the right side; thus, three ureters were catheterized. It will be noted that each ureter secreted nearly identical urine volumes, with equal sodium concentrations in each collection period—a negative test.

Case 8 (L. R.): The catheter study was considered to be negative in this patient, since the

reduction in urine volume was not significant, and the sodium concentration was greater on the "diseased" side.

Cases 7 and 8 had I¹¹ Diodrast renograms performed which were compatible with a decreased arterial flow to the left kidney. In each of these patients, renal arteriogram revealed a vascular abnormality in this same kidney. Nephrectomy was performed on the basis of the arteriographic findings.

No fixed criteria have been established for the interpretation of a "positive" catheterization test, but thus far the patient with the smallest differences from the two kidneys who obtained relief of hypertension by operation demonstrated a 50% reduction in urine volume and a 15% lowering of sodium concentration on this same side (table 1).

However, a set of circumstances is clearly conceivable in which 50% less urine flow from one kidney could be present and sodium concentration equal on the two sides, and still this kidney could be the offending agent. Since there is ample proof 12 that an ischemic kidney secreting no urine may cause hypertension, so, too, there might be hypertension resulting from ischemia of a segment of one kidney, which segment was secreting no urine. Urine coming from such a kidney should be of lesser volume than that from its normal partner, but should be qualitatively identical. There were two patients in this series with hypertension due to segmental renal ischemia wherein the ureteral catheterization studies disclosed exactly such findings. Since these results differ somewhat from those recorded in table 1, a detailed summary of the data on each of these patients is presented.

CASE REPORTS

Case 1. A 28 year old Negro male was admitted to The Johns Hopkins Hospital in May, 1959, for investigation of hypertension. Six months before hospitalization the patient had been kicked in the right flank in a fight. Gross hematuria was observed for a few days after the injury, and a blood pressure of 134/96 mm. of Hg was recorded at that time. One month before admission the patient noted increasingly severe headaches, and persistent hypertension was observed.

Physical examination was essentially negative except for sustained blood pressure readings of 150/110 to 190/140 mm. of Hg, and grade II hypertensive changes in the retinal vessels. Intravenous pyelogram was normal except that the right kidney was 1 cm. shorter than the left. Routine urinalysis revealed no abnormality. Phenolsulfonphthalein excretion was 45% in 15 minutes. An I¹³¹ Diodrast renogram (performed by Dr. Francis Chinard) revealed a lesser uptake of dye by the right kidney. Simultaneous ureteral catheterization studies were carried out, and the results are shown in table 4.

A renal arteriogram was performed, and no abnormality could be detected either in the renal arterial system or in the nephrogram. The patient was surgically explored and the lower half of the right kidney was found to be ischemic, due to an occlusion of one of the branches of the main renal artery. A heminephrectomy was not technically feasible, and the entire right kidney was therefore removed, with alleviation of hypertension during a three-month period of follow-up.

Case 2.* A 30 year old housewife was admitted to the University of Maryland Hospital in 1953 because of hypertension and leg cramps of three months' duration. Aortogram revealed a complete obstruction within the aorta, just below the level of the renal arteries. At surgical exploration a thrombus was removed from the aorta. It was also noted that each kidney was supplied by two renal arteries. The artery to the lower pole of the left kidney was occluded at its origin. This vessel was ligated and left heminephrectomy was performed. The patient's blood pressure

^{*}We are indebted to Dr. Leonard Scherlis and Dr. R. A. Cowley for allowing us to study this patient. A complete clinical summary on this patient will be reported by these authors at a later date.

100

102

101

103

H

50

48

| Date, 1959 Period | Period | | Volume in ml. | | Sodium mEq./L. | | | | |
|-------------------|--------|----------|---------------|---|----------------|--------------|---|--|--|
| | reriod | L | R | В | L | R | В | | |
| May 19 | II | 54 49 | 26 21 | 0 | 104 119 | 108* 124* | 0 | | |
| May 28 | I | 52 | 29 | 4 | 102 | 101 | | | |

28

30

10

promptly returned to normal, and remained between 120-130/80-90/mm. of Hg for the next four years,

In September, 1957, a blood pressure of 200/120 mm. of Hg was recorded when the patient consulted a physician for headaches. Hypertension persisted, and the patient was re-admitted to the hospital for study in March, 1958. Intravenous pyelogram was normal except for the absence of the lower pole of the left kidney. Ureteral catheterization studies were carried out, and the results are recorded in the upper half of figure 1. It will be noted that urine volumes and sodium concentrations were essentially identical from the two kidneys in three collection periods. Renal

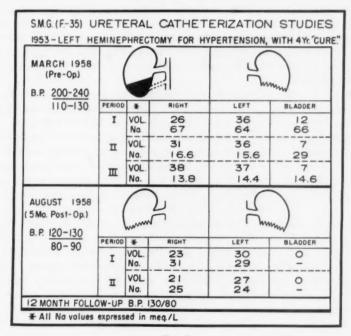


Fig. 1.

^{*} Any difference in sodium concentration less than 5% is not considered to be significant.

arteriography was performed, and the only abnormality noted was an absence of dye in the lower half of the right kidney, as outlined in the diagram at the top of figure 1.

On March 28, 1958, surgical exploration disclosed nearly complete occlusion of the artery supplying the lower pole of the right kidney. This vessel was ligated and a right heminephrectomy was performed. The blood pressure returned to 140/80 mm. of Hg within four hours after operation, and has remained in the range of 120–130/80–90 mm. of Hg during a 12-month period of follow-up.

Comment: Before the final operation in case 2 the ureteral catheterization studies were interpreted as "negative," since approximately equal urine volumes and sodium concentrations were obtained from each kidney (figure 1). On the other hand, arteriography revealed findings compatible with reduced arterial flow to the lower pole of the right kidney. This proved to be present at operation. How, then, could we explain the results of the catheter studies in this patient with documented unilateral renal ischemia?

It seemed reasonable that if the ischemic zone at the lower pole of the right kidney was secreting no urine, then on the catheter study we were measuring urine coming from the upper two thirds of each kidney, whose function was essentially normal. One should therefore expect to obtain equal volumes of urine with equal sodium concentrations from each kidney. If this were the case, then catheterization studies carried out postoperatively (when the patient was normotensive) should reveal essentially the same findings as the studies performed before operation. Examination of the results of the second catheter study, carried out five months after heminephrectomy (figure 1), does indeed reveal nearly identical urine volumes, with equal sodium concentrations from the two kidneys. This would seem to offer an adequate explanation for the results of the catheterization studies in this patient.

The studies in these two subjects emphasize that segmental renal ischemia may occur and cause hypertension, yet the simultaneous catheter study may reveal a 50% reduction in urine volume from the affected side with equal sodium concentrations. Although we would previously have called such tests "negative," and advised against nephrectomy, we now believe that any hypertensive patient with these results on the catheter study should have a renal arteriogram performed to aid in the detection of this possibility of segmental renal ischemia. It should be emphasized, however, that in one patient (case 1), renal arteriogram revealed no abnormality in the presence of a proved obstruction in a branch of the renal artery. Furthermore, the studies on case 2 emphasize that the function of the opposite, or "good," kidney may not always be normal, and this must be given consideration in the interpretation of simultaneous ureteral catheterization studies.

In addition to these two cases, the authors know of two other patients ^{16, 17} with segmental renal ischemia, in whom the catheterization study revealed 50% reduction in urine flow from one kidney, but equal sodium concentrations, and hypertension was relieved following removal of the kidney with lower urine output.

DISCUSSION

This high degree of accuracy in a biologic test involving so many possible mechanical and physiologic variables, must mean that the principles upon which it is based are sound. Other investigators have had similar experiences with this test. Yendt ¹⁶ in Toronto has studied 15 hypertensive patients wherein the ureteral catheterization test correctly predicted the postoperative result following nephrectomy or surgical correction of a renal arterial defect. Winter has reported similar results in two patients. ¹⁸

The results of the catheter studies in case 4 of Birchall et al., 19 wherein a reduced urine volume but higher sodium concentration were obtained from an ischemic kidney, are difficult to interpret, since a somewhat different technic was used. These investigators gave an infusion of inulin and sodium para-aminohippurate during the study. In one of the animal experiments of Mueller and associates, 13b and in two of our patients (table 1, cases 4 and 6), it appeared that infusions of sodium may alter the excretion of this ion by an ischemic kidney, thus vitiating the interpretation of the results. It is for this reason that the authors have emphasized that intravenous injections of sodium salts be omitted during simultaneous ureteral catheterization studies in hypertensive subjects. The variable results reported by Schlegel 20 likewise might be attributed to the use of similar infusion technics during the studies. However, it should be pointed out that in some of the studies reported by these investigators, 10, 20 the results were consistent with those reported herein, even though infusions of inulin and sodium para-aminohippurate were administered. Nevertheless, until more controlled observations are available in hypertensive subjects with unilateral renal ischemia, wherein studies are performed with and without such infusions in the same patient, the authors believe that these results must be interpreted with some reservation.

Likewise, it seems unwise to attempt interpretation on the same criteria when additional technical modifications have been used—for example, if a catheter has been placed in one ureter only, and bladder urine has been accepted as that derived from the opposite kidney.^{21, 22} Doubtless such technic has value, but the presence of a catheter or balloon in one ureter may provide physical differences between the two sides which could make for functional changes on a mechanical basis.

Simultaneous catheter studies are technically difficult to perform, time-consuming in manpower, and hardly pleasant procedures for the patient to undergo. We are still harassed by the question, "For which hypertensive patients do you recommend that the catheterization study be done?" We have been guided by certain clinical criteria, and perform the catheter study in hypertensive patients presenting these features:

1. Onset of hypertension before age 30 or after age 55.

2. Abrupt onset and rapid progression of hypertension at any age.

- 3. History of abdominal pain (unexplained) or renal trauma (surgical or accidental) just preceding onset of disease.
- 4. Sudden acceleration of preëxisting hypertensive disease.
- 5. Findings on intravenous pyelogram * (variable):
 - a. One kidney reduced in size.
 - b. Delayed excretion of dye by one kidney.
 - c. Absence of dye excretion by one kidney.

At the present time the authors believe that there must be at least a 50% reduction in urine volume from one kidney before unilateral ischemia can be considered. If, in addition, the urine sodium concentration is reduced by 15% or more from the same side with the reduced volume, this pattern appears to be diagnostic of ischemia. On the other hand, if the urine sodium concentrations are equal in the presence of a 50% reduction in urine volume from one kidney, segmental renal ischemia may be present. In this situation the authors believe that renal arteriography will usually be of assistance in diagnosis. However, in an occasional situation it may not be possible to exclude the presence of segmental renal ischemia without resorting to surgical exploration, as was demonstrated in case 1 (table 4).

It is our current belief that most patients for whom nephrectomy is contemplated for relief of hypertension probably should have renal arteriography performed if the catheterization study is "positive." This injunction is not based upon any idea that arteriography is diagnostic, at least in the sense here desired; for any atrophic tissue has reduced arterial flow, and reduced renal arterial flow per se is not necessarily conducive to hypertension. The authors are performing arteriography prior to renal surgery for the following reasons: (1) there are rare bilateral obstructing lesions of the renal arteries, 16, 22, 23 of congenital or acquired origin, which have given a "positive" catheterization test for unilateral disease, presumably due to a greater degree of ischemia on one side; (2) lesions may be disclosed which are amenable to plastic vascular surgery, and thus nephrectomy can be avoided; 24, 25 and (3) segmental ischemia may be disclosed in one kidney which will aid in interpreting the catheter study in some of the cases with equal sodium concentrations.

It will be noted in tables 1 and 2 that the renal arteriogram correlated rather well with the postoperative response in blood pressure, except in three instances (table 2, cases 7 and 8, and table 4). In two of these patients a renal arterial defect was present (radiographically and anatomically), yet no effect on hypertension was observed following nephrectomy. In the other subject (table 4), the arteriogram was interpreted as normal in the presence of a proved obstruction in a renal artery.

The use of I131-labeled Diodrast to determine relative arterial flow

^{*}In the authors' experience, the intravenous pyelogram has been entirely normal in 25% of hypertensive patients with *proved* unilateral renal ischemia.

through the two kidneys may well prove to be a highly useful screening procedure in expert hands, 18, 26 for, so far as we know now, no single kidney can induce hypertension unless there is ischemia to a sizable portion of its parenchyma. But, as with arteriography, this test will not indicate whether an existing reduction in arterial flow to one kidney is *causing* hypertension, as is evident from the studies on two of our own patients (table 2, cases 7 and 8).

In those patients in whom a "functionless" kidney, secreting no urine but with intact collecting systems (as judged by retrograde pyelogram), is found, there is as yet no way apparent to the authors of determining whether removal of this organ or plastic surgery will benefit the existing hypertension. If facilities for arteriography are available, the authors believe this study should be carried out with the hope that a renal arterial lesion amenable to vascular surgery will be found. Otherwise, nephrectomy is performed, provided the general condition of the patient warrants the surgical risk. Aortography is a valuable adjunct, but may be associated with serious complications in some instances.

Finally, we should like to summarize briefly some anatomic observations made on these patients. In all but one of the 11 patients benefited by nephrectomy or endarterectomy (table 1, table 4, figure 1), there was definite anatomic evidence of an obstruction in arterial flow to the affected kidney, as demonstrated by arteriography or surgical exploration. In the one patient in whom no such abnormality in a major renal vessel was found (table 1, case 4), microscopic examination of the excised kidney disclosed widespread areas of "ischemic" tubular atrophy adjacent to lesions typical of chronic pyelonephritis. Kincaid-Smith has presented similar histologic evidence in those patients with pyelonephritis who manifest an elevated blood pressure. 30 In this same group of patients who benefited, seven of the 10 kidneys that were removed likewise disclosed widespread areas of tubular atrophy of the "ischemic" type.* No parenchymal abnormality could be found in the kidneys removed from three patients in this group. In eight of the nine patients whose hypertension was not altered by operation (tables 2 and 3), the "ischemic" type of tubular atrophy was usually absent, or was present in very few scattered foci. Instead, these kidneys showed changes typical of chronic pyelonephritis, or moderately advanced to severe changes of arterial or arteriolar nephrosclerosis.12

SUMMARY

1. Studies of simultaneously collected urine from each kidney in hypertensive subjects have proved to be a valuable guide in distinguishing those abnormal kidneys which are responsible for hypertension from those which are not.

^{*}These histologic changes have been described in greater detail in previous reports by Berthrong. $^{5, 12}$

2. Criteria for the interpretation of these studies have been presented.

3. Detailed precautions have been outlined which must be observed for the performance of simultaneous ureteral catheterization studies.

4. Renal arteriography is a valuable adjunct aiding in the interpretation of some of the catheterization studies. It is especially helpful in determining the choice of surgical procedure required for relief of hypertension in these patients.

5. The functional pattern of reduced arterial flow to one kidney as demonstrated by ureteral catheterization studies correlated well with the anatomic evidence of renal ischemia and the response of the patients' blood pressure to nephrectomy.

ADDENDUM

Since submission of this manuscript the authors have studied a 41 year old woman with hypertension (170/110–180/130 mm. Hg) of two years' duration. Ureteral catheterization studies disclosed only a 45% lowering of urine volume from one kidney and a 25% reduction in sodium concentration on this same side. An obstruction in the main renal artery supplying this kidney was found at operation and nephrectomy was performed by Dr. J. D. Young. A separate artery arising from the main renal artery, proximal to the site of obstruction, was found supplying the upper pole of this kidney. The patient's blood pressure has been normal during a four-week period of follow-up.

Some additional information has also been obtained with regard to the use of osmotic diuresis during ureteral catheterization studies. Dr. H. L. White, Department of Physiology, Washington University, St. Louis, has reported (personal communication to the authors) that mannitol diuresis has masked sodium differences with the result that sodium concentrations were nearly equal in the urine from each kidney even in the presence of severe unilateral renal ischemia. This further emphasizes that infusion of such agents should be avoided when performing catheterization studies in hypertensive subjects if one wishes to interpret the test according to the criteria outlined by the authors.

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The authors are also indebted to the many physicians who permitted the studies to be carried out on these patients. We also wish to acknowledge the technical assistance of Mr. Harry Eisenberg and Miss Lillian Darago, who performed the sodium determinations reported herein. We are especially indebted to Dr. Morgan Berthrong, Dr. John Yardley, and Dr. Colin Wood for their histologic interpretations of the excised kidneys.

SUMMARIO IN INTERLINGUA

Le autores ha studiate plus que 200 subjectos hypertensive per medio del technica de simultanee catheterismo ureteral. In 58 patientes con hypertension essential, practicamente identic volumines de urina con concentrationes equal de natrium esseva obtenite ab le duo renes. In novem altere patientes, omnes con un reduction del volumine de urina ab un del renes amontante a al minus 50 pro cento e un reduction del concentration de natrium in le urina ab le mesme ren amontante a al minus 15 pro cento, un alleviation perdurative del hypertension esseva effectuate per interventiones chirurgic (Gruppo I). In octo de iste casos, le ren esseva excidite que secerneva le volumine plus micre de urina con le concentration plus basse de natrium. In le remanente caso de iste gruppo, endarterectomia renal esseva effectuate.

In octo altere subjectos hypertensive con morbo renal unilateral (indicate per un plus micre ren a un latere del pyelogramma intravenose), studios de catheterismo simultanee revelava un reduction del volumine de urina ab le latere afficite amontante a inter 30 e 90 pro cento, sed le concentrationes urinari de natrium esseva equal a ambe lateres o mesmo plus alte al latere con le reducite volumine. In omne iste casos le ren plus micre esseva excidite sin ulle effecto super le hypertension (Gruppo II). Un altere patiente con un reduction del volumine de urina ab un del renes amontante a inter 20 e 30 pro cento e un reduction de 30 pro cento in le concentration de natrium al mesme latere obteneva nulle alleviamento del hypertension post le excision de iste ren.

Arteriogrammas renal esseva effectuate in septe del novem patientes in Gruppo I, e in omne iste casos un obstruction del major arteria renal o le absentia de illo esseva demonstrate al latere morbide. In Gruppo II, arteriogrammas renal indicava un obstruction del major arteria renal provisionante le ren que esseva excidite in duo del casos. In istos, le constatationes arteriographic esseva le base del decision de effectuar nephrectomia.

Duo patientes con ischemia renal segmental exhibiva constatationes de catheterismo un pauco differente. In un, le volumine de urina esseva reducite per 50 pro cento al latere dextere, sed le concentrationes de natrium esseva le mesmes al duo lateres. Le arteriogramma esseva normal in iste patiente. Le intervention chirurgic revelava un obstruction de un branca del arteria alimentante le polo inferior del ren al latere dextere. Nephrectomia esseva effctuate con le resultato de un alleviation perdurative del hypertension. Simile constatationes de catheterismo esseva obtenite in un altere patiente in qui heminephrectomia sinistre habeva essite interprendite in 1953 pro le alleviamento de hypertension. In 1958, le hypertension recurreva, e studios de catheterismo ureteral a iste tempore revelava equal volumines de urina e equal concentrationes de natrium al duo lateres, i.e., le test esseva "negative." Arteriographia renal revelava un obstruction in le arteria alimentante le polo inferior del ren al latere dextere. Heminephrectomia al latere dextere esseva effectuate con le resultato de reversion a normotensivitate durante un periodo de observation sequential de 18 menses. Studios de catheterismo effectuate in iste patiente cinque menses post le heminephrectomia al latere dextere revelava essentialmente le mesme resultatos como illos observate ante le operation. Le duo ultimemente mentionate patientes servi a sublinear le facto que ischemia renal segmental pote occurrer con le resultato de un configuration in le datos del catheterismo que reflecte un reduction del volumine de urina a un latere amontante a 50 pro cento sed nulle differentia inter le concentrationes de natrium al duo lateres.

Le stato functional associate con reducite fluxos arterial a un del renes, in tanto que illo esseva reflectite in le resultatos del studios de catheterismo ureteral, monstrava un alte grado de correlation con le evidentia anatomic de ischemia renal e le responsa del tension sanguinee del patiente al effectuation de nephrectomia. Es presentate

criterios pro le interpretation de iste studios, insimul con un schizzo del detaliate precautiones que debe esser observate in lor effectuation.

Arteriographia renal es un importante adjuncto in le interpretation de certes del studios de catheterismo, specialmente in casos in que iste studios revela equal concentrationes de natrium al duo lateres. Arteriographia renal es specialmente utile in determinar le selection del typo de intervention chirurgic que es requirite pro alleviar le hypertension de iste patientes.

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ACTH-PRODUCING PITUITARY TUMORS FOLLOW-ING ADRENALECTOMY FOR CUSHING'S SYNDROME * †

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SINCE describing a single patient who, following bilateral adrenalectomy for Cushing's syndrome associated with adrenal hyperplasia, subsequently developed an ACTH-producing tumor of the pituitary gland, we have had the opportunity to study or to determine plasma-ACTH levels on a total of nine other similar patients.1 It is the purpose of this study to report one additional patient in detail, and to describe the clinical picture presented by these patients. Preliminary evidence concerning the therapy of this condition is also given. In none of the patients to be described was there evidence of a tumor of the pituitary gland prior to bilateral adrenalectomy, but the possibility cannot be ruled out that a very small tumor was present and subsequently grew to a larger and more easily demonstrable size.

METHODS

Patient C. R. was previously studied in detail, and complete data have been reported.2 Patient T. M. was likewise admitted to the Metabolic Ward of the Peter Bent Brigham Hospital, where special studies were carried out. Patient M. A. was seen at the Massachusetts General Hospital, where samples of plasma were drawn for ACTH assay and an attempt at suppression of plasma-ACTH levels by the administration of hydrocortisone was carried out. Other patients described in this study were hospitalized in a number of different medical centers, where plasma was drawn for ACTH determination according to our general procedure and shipped to us in the frozen state for assay. ACTH assays were carried out on 5- to 20-ml. quantities of heparinized plasma which had been separated immediately from cells by centrifugation, and frozen until the time the assay was carried out. Assay was performed in the hypophysectomized dog as described by Nelson and Hume.8

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CASE REPORT

T. M., a 26 year old white male, was admitted to the Peter Bent Brigham Hospital on March 21, 1958, for the first time. He had been adrenalectomized in November, 1955, at another hospital for Cushing's syndrome. Symptoms dated to 1950, at which time, while in the Army, he was told that he had hypertension, and he noted some gain in weight. When first admitted to the University of California Hospital, in September, 1955, he was complaining of generalized weakness, backache, polydipsia, decreased libido, polyuria, easy bruisability and poor wound healing. Significant findings at that time revealed a young white male with the typical picture of central obesity, moon-shaped plethoric face, and buffalo hump, characteristic of Cushing's syndrome. Blood pressure was 180/105 mm. Hg, and there were purplish striae over the lower abdomen. Laboratory findings were as follows: hemoglobin, 17 mg.%; hematocrit, 48%; white blood count, 7,000 cells per cubic millimeter; fasting blood sugar, 69 to 80 mg.%, with a mild diabetic-type glucose tolerance curve. X-ray examination revealed some demineralization of the thoracic spine and fractures of the right fifth rib, with compression of the vertebral bodies at T5 and T6. Retroperitoneal oxygen studies revealed bilaterally enlarged adrenal glands. An electrocardiogram showed left ventricular hypertrophy; 17-hydroxycorticosteroids had a base line value of 29 mg. which, after ACTH infusion, increased to 97 mg. per 24 hours. Base line 17-ketosteroids were 50 mg. per 24 hours which, after ACTH stimulation, increased to 104 mg. per 24 hours. Following the administration of fluorohydrocortisone in a dosage of 12 mg. per day, output of urinary 17-hydroxycorticosteroids fell to 15 mg. per 24 hours and 17-ketosteroids to 35 mg. per 24 hours. Adrenal exploration revealed bilateral adrenal hyperplasia, and both adrenals were removed. The patient was treated with 121/2 mg. of cortisone acetate three times a day orally. In January, 1957, this therapy was changed to hydrocortisone, 20 mg. twice a day, with 4 gm. of added sodium chloride. The patient appeared to be doing well when discharged for the second time. Following the operation, the blood pressure returned to normal values. The patient noted gradually increasing pigmentation, particularly over extensor surfaces of the buccal mucosa. He was admitted to the Peter Bent Brigham Hospital for a general check-up on the condition of his adrenal therapy on moving to this locality from California. He was a well developed, well nourished 26 year old white male in no distress. He was moderately obese. Temperature, pulse and respiration were within normal range. The blood pressure was 175/120 mm. Hg. The only remarkable physical finding, other than the scars at sites of removal of the adrenal glands, was a rather diffuse brownish tan with increased pigmentation, especially over the extensor surfaces of the limbs. There were many black freckles on the back, and there was rather marked bluish pigmentation of the lips and buccal mucosa. X-ray examination of the sella turcica, when compared with films taken at the University of California Hospital in 1955, showed definite expansion of the sella turcica. The following laboratory data were recorded: hematocrit, 47.5%; blood urea nitrogen, 16 mg.%; white blood count, 9,400 per cubic millimeter, with a normal differential; serum protein, 6.4 gm.%, with albumin, 4.4. Fasting blood sugar, 66 mg.%; cholesterol, 228 mg.%; sodium, 143 mEq./L.; potassium, 4.4 mEq./L.; CO₂, 25 mMoles/L.; chloride, 100 mEq./L. X-ray of the chest was within normal limits and of the thoracic spine showed wedging of the body of T7, and the vertebrae were thought to be of less than average density. Visual fields were normal. Blood ACTH determinations varied between 42 and 74 mU. (milliunits, U.S.P.) per 100 ml. of plasma. An attempt to suppress plasma-ACTH with 20 mg, of hydrocortisone given intravenously over a period of four hours resulted in a fall in measurable ACTH from a level of approximately 28 mU, per 100 ml. of plasma to a level of 7 mU. per 100 ml. of plasma. It was decided to irradiate the

enlarged pituitary gland. The patient received irradiation through five portals for a total estimated tumor dose of 2982 roentgens over the period September 19, 1958, to October 4, 1958. Seven months following the completion of irradiation, the plasma-ACTH was 60 mU. per 100 ml. of plasma, and there was no evidence of decrease in pigmentation.

RESULTS

The results of 16 determinations for plasma-ACTH in the 10 patients described are shown in figure 1. It can be seen that, with one exception, all of the ACTH determinations are above the range of values found in patients with Addison's disease. The three highest values are taken from the first patient, who was previously reported.² In contrast, the ACTH levels of five patients with adrenal hyperplasia and Cushing's syndrome in whom determinations of plasma-ACTH were made prior to adrenalectomy were not elevated, with one exception, which is noted in figure 1 as a patient with partial adrenalectomy. This patient underwent partial adrenalectomy

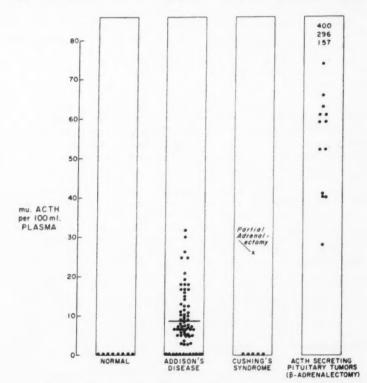


Fig. 1. Plasma-ACTH levels in normal subjects, and in patients with Addison's disease and Cushing's syndrome, and in a group of patients who have developed pituitary tumors following adrenalectomy for Cushing's syndrome.

SUPPRESSION OF PLASMA ACTH WITH I.V. HYDROCORTISONE

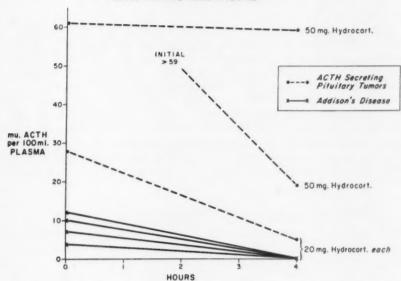


Fig. 2. Changes in plasma-ACTH occurring in patients with Addison's disease and ACTH-producing pituitary tumors following intravenous infusion of hydrocortisone.

with temporary remission of Cushing's syndrome, and then returned with recurrence of the disease and an associated enlargement of the sella turcica. At this time the plasma-ACTH level was found to be 25 mU. per 100 ml. of plasma, and the urinary 17-hydroxycorticosteroids to be 17 mg. per 24 hours. In no other case was an elevation of plasma-ACTH found in association with elevated urinary 17-hydroxycorticosteroids. It should be noted also in figure 1 that it has not been possible with the present technic to detect normal circulating levels of plasma-ACTH, and therefore a slight elevation of ACTH above "normal" would presumably not be detected by the assay procedure used.

Figure 2 illustrates an attempt made to suppress plasma-ACTH in four patients with Addison's disease and three patients with ACTH-secreting pituitary tumors. The four lower solid lines are in agreement with work previously reported by Bethune et al., that 20 mg. of hydrocortisone given over a four-hour period to Addisonian patients will in almost all cases cause suppression of plasma-ACTH levels to a nondetectable level. In two cases of pituitary tumor, one given 20 mg. and one given 50 mg. of hydrocortisone intravenously over a four-hour period, it was possible to cause a reduction in the circulating levels of ACTH, but in neither case did the level of ACTH fall to a nondetectable value in the four-hour period of study. In a third

patient (case M. A.), there was no demonstrable suppression of plasma-ACTH when 50 mg. of hydrocortisone were given intravenously over a four-hour period.

As the patients included in this study had been seen by a number of different physicians at the time the diagnosis of Cushing's syndrome was made, and as the adrenalectomies were carried out in a number of different hospitals, it was not possible to obtain complete information concerning their status prior to adrenalectomy. The available data on these patients, however, are summarized in table 1. It may be seen that in each case where urinary corticosteroids were measured, a definite elevation was obtained; however, in one case the diagnosis was made prior to the general availability of such determinations, and thus no urinary corticosteroids were measured. In three cases where an attempt was made to suppress endogenous corticosteroid production by the administration of one of the potent corticosteroids

Table 1

Response to ACTH Stimulation and Steroid Suppression Prior to Adrenalectomy in Patients Later Found to Have Pituitary Tumors

| Name | Elevated Urinary Corticosteroids | Suppression by Corticosteroids | Response to ACTH |
|-------|-------------------------------------|-----------------------------------|------------------|
| C. R. | Yes | Yes | Yes |
| T. M. | Yes | Yes | Yes |
| M. A. | | - | _ |
| B. B. | Yes | | Yes |
| M. K. | Yes | | Yes |
| G. K. | Yes | Yes | Yes |
| A. S. | Yes | | Yes |
| P. H. | Yes | ****** | |

such as $9-\alpha$ -fluorohydrocortisone, it was possible to produce such suppression; and in six cases where ACTH was administered to the patient, there was a brisk response to exogenous ACTH. In no case was there evidence of pituitary abnormality by x-ray examination of the skull, but this was carried out in only seven of the 10 cases prior to adrenalectomy.

Table 2 demonstrates the effect of irradiation of the pituitary gland or hypophysectomy plus irradiation upon circulating levels of ACTH in the plasma of three of these patients, who have been followed for a period of from five to 15 months. It is noted that case C. R., who had a partial hypophysectomy followed by 3,010 roentgens to the pituitary gland, had a marked fall in plasma-ACTH, which has remained within the "normal" range for an Addisonian or bilaterally adrenalectomized patient for a period of 15 months. In this patient, menstrual periods had returned to normal, improvement of visual fields was noted, and a marked decrease in pigmentation had occurred. Case T. M., who received irradiation to the pituitary gland consisting of 3,000 roentgens to the region of the pituitary tumor, had an elevated ACTH-plasma level prior to irradiation which approximately five

months later is still in the elevated range, and although the patient has moved to another city, we are told that the pigmentation is as deep as or deeper than previously. The third patient seen in table 2 (M. A.) received 4,100 roentgens to the region of the pituitary gland, with no demonstrable effect on plasma levels of ACTH at a period five months following therapy. In four patients who had received x-ray therapy prior to determination of plasma-ACTH, no elevation of plasma-ACTH was found. In each case an enlarging sella turcica was seen, and the characteristic marked increase in pigmentation was also present. In at least one of these patients, a marked decrease in pigmentation occurred following additional irradiation of the pituitary gland.

It is of interest that, in two patients in whom histologic examination of the pituitary gland was available, a chromophobe tumor was reported to be present.

TABLE 2
Effect of Pituitary Irradiation on Plasma-ACTH Levels (mU./100 ml.) in Three Patients

| | C. R. Hypox. + X-Ray (3,010r to pit.) | T. M. X-Ray (3,000r to pit.) | M. A. X-Ray (4,100r to pit.) |
|--|---------------------------------------|---------------------------------|---------------------------------|
| Before Therapy Months after Therapy | 150-400 | 42-74 | 52-61 |
| 1 2 | 20 10 | 52 | |
| 3 | 10 | | 40 |
| 5 7 | 4 | 60 | 57 |
| 15 | 18 | 55 | |

DISCUSSION

The evidence presented here would appear to strengthen the view that Cushing's syndrome associated with adrenal hyperplasia is due to increased production of ACTH by the anterior pituitary gland. Thus, although it is not possible to say definitely whether these tumors were present in the pituitary gland prior to adrenalectomy or appeared following the removal of the adrenal cortices, such tumors have been seen only in patients who have been adrenalectomized for adrenal hyperplasia. No tumors have been reported in patients who have had adrenal adenomas removed, or in patients adrenalectomized for hypertension or carcinoma, which strongly suggests either that the tumor was present prior to bilateral adrenalectomy, or that there was some abnormal stimulus to the pituitary gland which may have acted to produce the pituitary adenoma in these particular cases. Production of pituitary tumors following removal of the adrenal glands would be analogous to the production of such tumors in mice, as described by Furth or Dickie and Wooley, following irradiation of the thyroid gland

or gonadectomy. It is hoped that application of newer methods, with greater sensitivity for measuring plasma-ACTH than those employed in this and previous studies, will answer the question as to whether plasma-ACTH levels are elevated in patients with Cushing's syndrome associated

with adrenal hyperplasia.

It should be pointed out that the patients in this study were maintained on normal replacement cortisone therapy following adrenalectomy. In most cases this consisted of 37 to 50 mg. of cortisone, given in one to three doses over a period of 24 hours. Although it has been well demonstrated that this quantity of cortisone will adequately maintain adrenalectomized or Addisonian subjects, it is known that this type of therapeutic program does not necessarily suppress ACTH levels over an entire 24-hour period. Thus, Bethune et al. found that plasma-ACTH was generally elevated 24 hours following the last dose of corticosteroid, and that a single infusion of 20 mg. of hydrocortisone over a period of four hours would not induce suppression of peripheral plasma-ACTH levels for longer than from six to eight hours in some subjects.4 It seems likely, therefore, that most patients receiving one or two doses of cortisone a day do not have complete suppression of pituitary production of ACTH. As mentioned above, however, patients who did not have previously existing Cushing's syndrome, who have developed Addison's disease or had adrenalectomy for other conditions, have not been noted to develop tumors of the pituitary gland.

The relatively small group of patients and the short period of observation do not permit an adequate discussion of therapeutic approach to these patients at this time. In the three patients who have been followed most closely, however (C. R., T. M. and M. A.), it can be seen in table 2 that only in the case of C. R., who was partially hypophysectomized in addition to receiving irradiation to the pituitary gland, has there been a significant fall in peripheral plasma-ACTH levels or a marked improvement in the clinical condition. Both patients T. M. and M. A. have continued to be deeply pigmented, and pituitary ACTH levels have remained at a very high level. It is certainly of interest that in at least one other case there has been a marked decrease in pigmentation following irradiation of the pituitary gland, and ACTH levels are now in the normal range, but in this case no plasma-ACTH determination was carried out prior to the pituitary irradiation.

Until better methods for the determination of MSH become available, it will probably not be possible to determine whether these pituitary tumors secrete MSH in addition to ACTH. All ACTH preparations apparently possess some MSH activity, and it is possible that the inherent MSH activity within the ACTH molecule is responsible for the skin pigmentation so typical of these cases. The close chemical similarity between ACTH and MSH is illustrated in figure 3.7

Pathologic reports on the two cases described in this series, where pituitary tissue has been removed surgically, indicate that these are chromo-

STRUCTURE OF ACTH AND MSH

(PORCINE)

Asp. Glu. Gly. Pro. Tyr. Lys. Met. Glu. His. Phe. Arg. Try. Gly. Ser. Pro. Pro. Lys. Asp. I 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

B - MSH

Ser. Tyr. Ser. Met. Giu. His. Phe. Arg. Try. Gly. Lys. Pro. Val. Gly. Lys. Lys. Arg. Arg. Pro. Val. I 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 Lys. Val. Tyr. Pro. Asp. Gly. Ala. Glu. Asp. Glu (NH₂). Leu. Ala. Glu. Ala. Phe. Pro. Leu. Glu. Phe. 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 3-4 C T H

| B-MSH | Pro. | Tyr. | Lys. | Met. | Glu. | His. | Phe. | Arg. | Try. | Gly. | Ser. | Pro. | Pro |
|--------|------|------|------|------|------|------|------|------|------|------|------|------|-----|
| D-MISH | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
| B-ACTH | Ser. | Tyr. | Ser. | Met. | Glu. | His. | Phe. | Arg. | Try. | Gly. | Lys. | Pro. | Vol |
| D-MCIH | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |

Fig. 3. Structure of β -ACTH and β -MSH, demonstrating the similarity in amino acid sequence between numbers 5 and 15 in the MSH molecule and 2 and 12 in the ACTH molecule. (Based on data from Behrens, O. K., and Bromer, W. W. 7)

phobe adenomas of the pituitary gland. These tumors may be similar to the chromophobe pituitary tumors which have been seen by Furth following irradiation of mice. These tumors, appearing in the pituitary gland of irradiated mice, have been shown to produce ACTH in excess quantity during in vitro incubation. It is of interest that a patient who appears to have a condition similar to those described in this report is stated to have a "mucoid cell adenoma (basophil adenoma)." ⁸ The finding of chromophobe tumors producing increased quantities of ACTH is, of course, not in agreement with the original statement by Cushing that basophil adenomas may commonly be found in Cushing's disease.

SUMMARY

Ten patients, previously adrenalectomized for Cushing's syndrome, who have subsequently developed evidence of a disturbance of the pituitary gland, have been studied. All of these patients were very deeply pigmented. In eight cases a tumor of the pituitary gland was demonstrable either by roent-genologic examination or by such evidence plus restricted visual fields. In two cases, markedly elevated levels of ACTH were found in association with deep pigmentation, but no tumor of the pituitary was demonstrable. In five of the 10 patients it has been possible to demonstrate a level of plasma-ACTH above that usually observed in Addisonian patients, or in other patients in whom a bilateral adrenalectomy has been carried out. All five patients who

did not have elevated levels of plasma-ACTH, but who were deeply pigmented and who did have evidence of pituitary tumors following adrenalectomy for Cushing's syndrome, had received irradiation to the pituitary gland prior to the time that the first plasma was obtained for ACTH assay. The average time from adrenalectomy to the appearance of the pituitary tumor has been three years, with a range of from one to eight years, and, as noted above, pituitary histologic examination in two cases has been reported to show cells of a "chromophobe type."

ACKNOWLEDGMENTS

The authors are indebted to the following physicians, who supplied clinical data and plasma samples for ACTH determination from patients under their care: Dr. K. Emerson, Jr., Dr. S. S. Fajans, Dr. D. H. P. Streeten, Dr. H. W. Moser, Dr. A. P. Forbes, Dr. R. M. Blizzard, Dr. J. J. Van Wyk, Dr. T. F. Williams, Dr. P. H. Forsham and Dr. T. F. Frawley.

SUMMARIO IN INTERLINGUA

Tumores pituitari esseva trovate in dece patientes 1 a 8 annos post adrenalectomia pro syndrome de Cushing. In omne iste casos, nulle tumor habeva essite notate ante le adrenalectomia, sed il non es possibile declarar categoricamente que nulle tal habeva essite presente e habeva escappate al detection ante le adrenalectomia. Marcate grados de pigmentation generalisate esseva presente in omne iste patientes; in un del casos il occurreva un rapide reduction del excesso de pigmentation post le ablation del tumor pituitari. Le determination del ACTH del plasma in iste patientes revelava valores variante inter 50 e 400 milli-unitates per 100 ml. Iste valores es marcatemente plus alte que le valor medie de 8 milli-unitates per 100 ml de plasma que ha essite trovate in altere patientes adrenalectomisate o addisonian.

On sape que le administration de 20 mg de hydrocortisona in le curso de 4 horas supprime completemente le ACTH in le plasma de patientes con morbo de Addison. Le administration de iste o mesmo un plus grande quantitate de hydrocortisona al patientes con tumores pituitari secernente ACTH causava nulle o solmente un partial suppression del ACTH plasmatic. Le irradiation del glandula pituitari produceva nulle significative effecto super le secretion de ACTH in duo patientes tenite sub observation durante periodos de 5 a 15 menses, sed in un caso le valores del ACTH plasmatic ha retornate a nivellos normal post hypophysectomia partial e irradiation pituitari.

Iste constatationes es compatibile con le conception que un tumor del glandula pituitari esseva responsabile pro le disveloppamento de syndrome de Cushing in iste patientes. Il pare que le tumor pituitari continuava crescer post le adrenalectomia e secerneva quantitates augmentate de ACTH. Le augmento del pigmentation esseva possibilemente le effecto del activitate melanino-stimulante del molecula de ACTH o forsan etiam de un concomitante augmento del secretion de hormon melanino-stimulante del tumor pituitari.

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OSTEOPOROSIS IN CUSHING'S SYNDROME *

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OSTEOPOROSIS is a striking and serious feature of Cushing's syndrome. This manifestation of the disease is evidenced by the demineralization seen on the roentgenogram, and by the frequent occurrence of pathologic fractures. Indeed, the collapse of the weakened vertebrae causes shortness of stature and contributes to the characteristic truncal obesity of the patient with this disease. It has been known for many years that, following cure of the disease, further collapse of the vertebrae ceases and pathologic fractures no longer appear. However, there are scant data as to what occurs in the bony skeleton following successful treatment of the disease. This report is concerned with the long-term follow-up in 10 patients with cured Cushing's syndrome in whom the roentgen demonstration of demineralization was apparent in varying degrees during the period of active disease.

METHODS

Repeated roentgen examinations were performed at varying periods following cure of the disease. In this study, evaluation was focused on the lumbar spine. It was realized that a possible error in interpretation could occur because of differences in the roentgen technic on separate examinations. A determined effort was made to avoid this trap, and interpretations were made only on the basis of unequivocal evidence.

At the time of treatment for their disease, the patients varied in age from 11 months to 46 years. The follow-up period varied from two to $12\frac{1}{2}$ years. In some instances the original films had been destroyed, and the filed reports (SAB) were used as the basis for comparison with recent films.

RESULTS

Case 1. An 11 month old child developed Cushing's syndrome at approximately three months of age, and during the eight-month interval growth was retarded.

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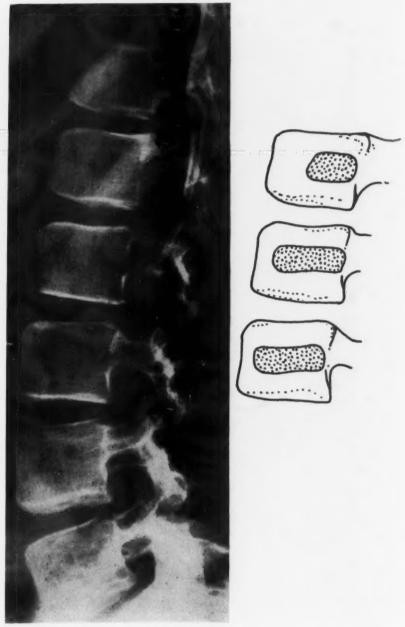


Fig. 1. Age 12½ years. Cushing's syndrome due to adrenal carcinoma cured at one year of age. Note areas of demineralization in center of vertebrae. Particularly in L1, the rarefied area resembles the vertebra of a young child.



Fig. 2A and B. Age 22 years. Cushing's syndrome due to adrenal adenoma cured seven years previously. Note that the vertebrae still exhibit concave upper and lower surfaces and some narrowing. The central demineralized area is sharply delineated from the more normal bone on its upper and lower surfaces.



Fig. 2B.

Roentgen examination revealed demineralization of the bones of the extremities. A carcinoma of the right adrenal was found and removed. Reëxamination at the age of 121/2 years revealed a girl of normal appearance who had no complaints. The height was 601/4 inches. Roentgen examination of the lumbar spine showed demineralization in the center of the vertebrae. The areas of demineralization resembled the vertebrae of a one year old child. The surrounding bone was normal (figure 1).

Case 2. A 15½ year old girl had had symptoms of Cushing's syndrome since the age of 11. Her height was 54 inches, having been 56 inches three and one-half years prior to admission. Roentgenography of the dorsolumbar spine, pelvis, ribs, long bones of the upper and lower extremities, and the skull revealed marked demineralization in all the bones examined. This was especially noted in the spine, where there were many compression fractures. In the ribs there were numerous fractures exhibiting excessive callus formation. The serum calcium was 11.1 mg.%; phosphorus, 2.2 mg.%, alkaline phosphatase, 16.5 King-Armstrong units.

Treatment for the nontumorous hyperfunction of the adrenal cortex consisted of right adrenalectomy and pituitary irradiation. Complete remission of the disease

When seen seven years later the patient had no skeletal complaints. Reëxamination of the spine at this time revealed a central area of demineralization surrounded at the upper and lower vertebral borders by normal bone (figure 2). The alkaline

phosphatase was 9.2 King-Armstrong units.

Case 3. A 28 year old woman had had signs of Cushing's syndrome for three years and low back pain for two years. During this period her height had decreased by 4 inches, and she was no longer able to walk. Roentgen examination of the skeleton revealed compression of practically all of the lumbar vertebrae and several of the dorsal vertebrae. The twelfth dorsal vertebra was collapsed to about one third, the eighth to one-half its normal size. The first, second and fourth lumbar vertebrae were also markedly compressed. Practically all of the ribs showed fractures, with excessive callus formation, and some of the ribs exhibited multiple fractures. All of the bones of the skeleton showed distinct decalcification, and fractures of the sternum and right ischium were present. The serum calcium was 10.8 mg.%; phosphorus, 3.1 mg.%; alkaline phosphatase, 23 King-Armstrong units. A right cortical adenoma was removed. Following cure of the Cushing's syndrome, the patient experienced only occasional back pain. Roentgen examination of the spine 10 years after removal of the tumor revealed persistent demineralization (figure 3). The serum alkaline phosphatase was 7.0 King-Armstrong units.

Case 4. A 33 year old woman had had symptoms of Cushing's syndrome for eight years, including severe pains in the lower posterior thorax, especially on motion. Roentgen examination revealed compression fractures of D6, D8, D9 and L1, with a resultant kyphotic deformity. The remaining vertebral bodies were markedly decalcified. To a lesser extent this was true of the pelvis, long bones and skull. The serum calcium was 10.0 mg.%; phosphorus, 3.6 mg.%; alkaline phos-

phatase, 16.3 King-Armstrong units.

Following pituitary irradiation the patient was cured of the manifestations of

Cushing's syndrome.

When seen 12 years later she had practically no complaints referable to the back. Skeletal survey revealed marked demineralization, unchanged from that noted prior to treatment (figure 4). The serum calcium was 10.1 mg.%; phosphorus, 2.7 mg.%;

alkaline phosphatase, 5.6 King-Armstrong units.

Case 5. A 28 year old woman had had symptoms of Cushing's syndrome for two years. Four years prior to admission she had had a roentgen examination of the lumbosacral spine because of "sciatic pain." It revealed (figure 5A) normal mineralization of the bone and mild productive changes about the articular margins.



Fig. 3. Age 38 years. Cushing's syndrome due to adrenal adenoma cured 10 years previously. Lumbar spine showing old compression fractures and persistent demineralization and loss of normal trabecular pattern.

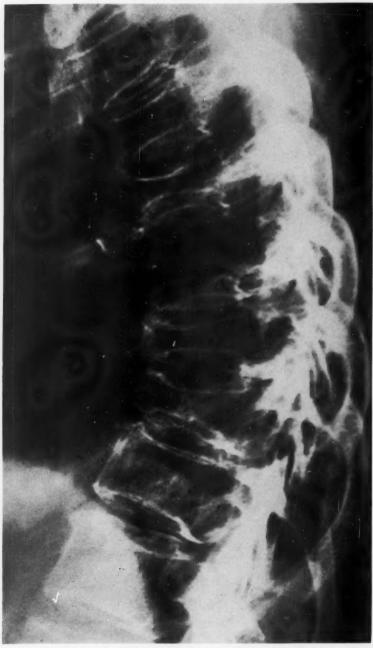


Fig. 4. Age 45 years. Cushing's syndrome due to nontumorous hyperplasia cured 12 years previously. (A) Thoracic spine.



Fig. 4 (B) Lumbar spine. The old compression fractures, severe demineralization and loss of normal trabecular pattern are seen.



Fig. 5. Age 36 years. Cushing's syndrome due to nontumorous hyperfunction of the adrenal, cured following pituitary irradiation eight years previously. (A) Lumbar spine, taken two years prior to symptoms of Cushing's syndrome. Note normal bone.



Fig. 5 (B) Lumbar spine, taken during active Cushing's syndrome. Note demineralization.



Fig. 5 (C) Lumbar spine, four years following cure of Cushing's syndrome.



Fig. 5 (D) Lumbar spine, eight years following cure of Cushing's syndrome. The roentgen technic is somewhat different. The original plates demonstrate the demineralization more clearly.

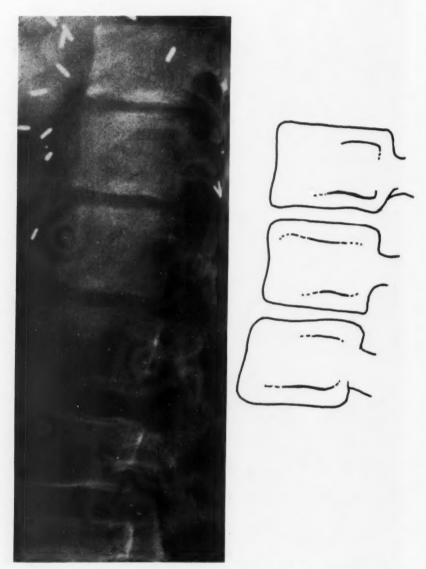


Fig. 6. Age 17 years. Cushing's syndrome treated at the age of 15 years. Note demineralization of vertebrae and the more normal bone laid down by the epiphysial end plates.

At the time of admission, x-ray examination of the lumbosacral spine revealed moderate generalized osteoporosis and compression of D9 and, to a lesser extent, D12 and L1 (figure 5B). The serum calcium was 10.7 mg.%; phosphorus, 2.7 mg.%; alkaline phosphatase, 10 King-Armstrong units.

The patient was treated with pituitary irradiation, with complete remission of the Cushing's syndrome.

Four years later she still complained of back pain. Roentgen examination revealed persistent demineralization of all the bones. The superior and inferior plates of L1, L2 and L3 showed some concavity (figure 5C).

Eight years following treatment the back pain was still present. X-ray examination of the spine revealed no change in the degree of demineralization (figure 5D). The serum calcium was 9.0 mg.%; phosphorus, 2.2 mg.%; alkaline phosphatase, 8.4 King-Armstrong units.

Case 6. A 15 year old boy had had symptoms of Cushing's syndrome for one year. He had never experienced back pain. X-ray examination of the skull and spine revealed mild osteoporosis. He was treated with pituitary irradiation and unilateral adrenalectomy and had a complete clinical remission. Two years later, roentgen examination revealed demineralization of the midportions of the lumbar vertebrae. These areas were sandwiched within normal appearing bone on the superior and inferior surfaces at the site of the end plates (figure 6). The appearance resembled to a mild degree that seen in case 2.

Case 7. A 23 year old woman had had symptoms of Cushing's syndrome for four years. Roentgen examination revealed a generalized demineralization of the vertebral column and some demineralization of the calvarium. The serum calcium was 10.5 mg.%; phosphorus, 2.9 mg.%; alkaline phosphatase, 10.4 King-Armstrong units. Two years following total adrenalectomy, roentgen examination revealed persistent demineralization. The calcium was 9.6 mg.%; phosphorus, 3.5 mg.%; alkaline phosphatase, 6.8 King-Armstrong units.

Case 8. A 36 year old woman had had symptoms of Cushing's syndrome for three years, and complained of severe back pain. Roentgen examination revealed a considerable degree of demineralization of the dorsolumbar-sacral spine and demineralization of the posterior clinoids of the skull. The serum calcium was 11.0 mg.%; phosphorus, 3.0 mg.%; alkaline phosphatase, 10 King-Armstrong units. Complete remission was induced by unilateral adrenalectomy and pituitary irradiation. Two years later the back pain had completely disappeared. Roentgen examination revealed the spine to be unchanged in appearance as compared to the period prior to treatment. The serum alkaline phosphatase was 8 King-Armstrong units.

Case 9. A 36-year old woman had had symptoms of Cushing's syndrome for two years. There was no history of backache, Roentgen examination revealed generalized osteoporosis with evidence of previous fractures of the pelvis and several ribs. Complete remission was induced following pituitary irradiation. Ten years later, roentgen examination revealed persistent demineralization.

Case 10. A 46 year old woman had had signs of Cushing's syndrome for one year. She had had occasional back pain. Roentgen examination revealed a moderate generalized demineralization of the bones. There were fractures in the ribs and ischium. The serum calcium was 10.9 mg.%; phosphorus, 3.1 mg.%; alkaline phosphatase, 10 King-Armstrong units. Following pituitary irradiation and unilateral adrenalectomy, a gradual remission of the disease ensued. The patient lost all symptoms referable to the back. Roentgen examination four years after treatment revealed persistent demineralization.

The serum calcium was 11 mg.%; phosphorus, 3.3 mg.%; alkaline phosphatase, 5.3 King-Armstrong units.

DISCUSSION

Recently Skeels 1 reported a case of Cushing's syndrome in an 11 year old girl with severe osteoporosis and multiple fractures. Four years following cure by means of bilateral subtotal adrenalectomy and pituitary irradiation, there was observed "remineralization and more normal contours of the vertebral bodies." It was difficult from the reproductions to note details of the bone structure, but certainly the vertebrae were higher and more calcified. Moldawer 2 pointed out that the case resembled one reported by Albright and Reifenstein.3,4 This latter patient also was an 11 year old child in whom "osteoporotic bone remained visible at the core of the vertebrae" but "new and normal bone was evident along the superior and inferior borders of the osteoporotic vertebrae." Moldawer claimed that remodeling of bone does not take place in the vertebrae as it does in long bones, and that therefore reversibility of osteoporosis in the former location does not occur. Howard 5 put forward the explanation that in bony areas surrounded by cartilage (endochondral bone formation), osteoporosis persists for long periods. He offered, as another example, the situation found in scurvy. He feels these endochrondal areas have a lower metabolic activity than do other bones not completely surrounded by cartilage.

Skanse and his associates ⁶ reported three instances of Cushing's syndrome with osteoporosis. In one, vertebral compression had occurred; in two this was not observed. They state that following successful treatment of the disease the osteoporosis improved in the latter two but not in the former.

However, our data would tend to support the thesis that, once osteoporosis of the bony vertebrae develops in the course of Cushing's syndrome. the affected bone remains demineralized indefinitely following cure of the disorder. In those instances which occur postpuberally, i.e., when the bony structure of the vertebra has been completely formed, the entire vertebra remains demineralized. In the cases here reported this was observed for periods of 8, 10 and 12 years following cure in patients with collapsed vertebrae, and for periods of two, two, four and 10 years, respectively, in patients in whom a lesser degree of osteoporosis and demineralization was present. However, if the epiphysial cartilaginous end plates are still present, then, following cure of the disorder, normal bone is laid down on the upper and lower surfaces of the vertebra. The resultant picture is that of a sandwich of normal bone encasing demineralized bone (figures 1, 2 and 6, and the figures reported by Albright 3, 4 and Skeels 1). It is of note that our studies represent follow-up periods of 11, eight and two years following remission of the disease, whereas the patients of Skeels and of Albright were followed for four and 12 years, respectively.1,2

In the pathologic studies available on the bone changes in active Cushing's syndrome ⁷ it has been noted that osteoclasts are absent. Osteoid

borders are scarce, and there is diminished osteoblastic activity on the bony surfaces. In growing epiphysial cartilage, Follis ⁸ noted arrest of growth and disorganization of the cartilage. It would seem that in Cushing's syndrome, once the bony structure of the vertebra is laid down and then destroyed, demineralization persists. There are no data to suggest whether this is due to the failure of osteoid deposition to occur, or failure to remineralize deposited osteoid. Certainly protein is laid down in the subcutaneous tissue following remission of the disease. However, it is possible that affected bone may react in a different fashion. On the other hand, following arrest of the disease the epiphysial cartilage plate can lay down normal bone. Whatever processes occur in bone following the induction of

Table 1
Serum Alkaline Phosphatase in Cushing's Syndrome
(King-Armstrong Units per 100 ml.)

| tring the beautiful and the second | | | |
|------------------------------------|--------------|-------------------|--|
| Case No. | Pretreatment | Posttreatment | |
| 1 2 | 16.5 | 9.2 | |
| 3 4 5 | 23 10.4 | 7.0 | |
| 6 | 16.3 10 | 6.8 5.6 8.4 | |
| 8 | 10 | 8 | |
| 10 | 10 | 5.3 | |

remission of the disease, successful therapy is attended by arrest of progression of the demineralization and osteoporosis and collapse, and usually by relief of the symptoms due to osteoporosis.

In view of the effect of Cushing's syndrome on bone, it is of interest to note that the serum alkaline phosphatase was elevated in three of the patients prior to treatment. Following remission, the levels returned to normal values (table 1). In a series of 34 patients with Cushing's syndrome, we found the serum alkaline phosphatase to be elevated in half of the 22 patients with osteoporosis, and normal in all 12 without osteoporosis.

SUMMARY

In Cushing's syndrome, osteoporosis is a common finding and may progress to a severe degree, resulting in vertebral collapse. Following cure of the disease, the demineralization demonstrable by roentgenography may persist indefinitely. However, in the growing child, normal bone will be laid down by the epiphysial end plates of the vertebrae around the previously and probably permanently altered bone.

SUMMARIO IN INTERLINGUA

Dece patientes con syndrome de Cushing e osteoporosis esseva studiate durante periodos de inter duo e 12½ annos post lor curation pro evalutar le effecto del tractamento super le comportamento del ossos. Roentgenoscopia esseva usate pro iste objectivo, e le attention esseva concentrate super le spina lumbar. Le patientes variava in etate inter 11 menses e 46 annos al tempore del tractamento de lor morbo.

Post le curation del syndrome de Cushing, le osteoporosis persisteva indefinitemente. Quando le disordine occurreva a un etate ante le complete formation ossee del vertebra, le jam formate portion vertebral que esseva dismineralisate in consequentia del morbo remaneva osteoporotic post le curation. Tamen, osso normal esseva deponite in le vertebra in le region del placas epiphysee post le successo del effortio de inducer un remission del morbo.

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SELECTED PROBLEMS IN ELECTRO-CARDIOGRAPHY * †

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DURING the course of routine interpretations of electrocardiograms, tracings are sometimes encountered which are difficult to interpret. The limitations in interpretation become evident if the patients are followed to autopsy. There are many aspects of electrocardiography which remain vague. Nevertheless, being responsible for his patient, the clinician must make every effort to obtain as much useful information as possible from the data accumulated in the clinical study. Classic electrocardiographic changes are easy to recognize and to relate properly to the clinical state of the patient, but tracings which fail to demonstrate configurations characteristic of the underlying cardiac disease can be erroneously interpreted and can mislead the physician who relies too much upon the tracing. The objective of the clinician should be to know the applications and limitations of these recordings in the diagnosis and management of his patient. To illustrate some of the difficulties in relating electrocardiographic configurations to the underlying cardiac state, 10 electrocardiograms are presented with clinical and autopsy data.

Electrocardiograms 1, 2 and 3 should be considered as a group because they are related.

Electrocardiogram 1 (figure 1) was of a 62 year old white male who had suffered from allergic bronchial asthma, emphysema and chronic bronchitis for many years. The electrocardiogram was considered to show cor pulmonale and to be compatible with that encountered in emphysema and with hypertrophy of the crista supraventricularis. This interpretation was supported by the large peaked P waves in Leads 1, 2 and 3, the wide, slurred and relatively prominent S waves in Leads 1, V₅ and V₆, and the relatively small notched and slurred S waves in V₁ and V₂.

At autopsy the heart weighed 420 gm. The free wall of the left ventricle was 30 mm, thick and the wall of the right ventricle was 10 mm, thick. There was marked right and left ventricular hypertrophy, as well as hypertrophy of the crista supraventricularis and of the right atrium.

Comment: Although the other clinical data indicated right and left ventricular hypertrophy, the electrocardiogram was interpreted as showing little

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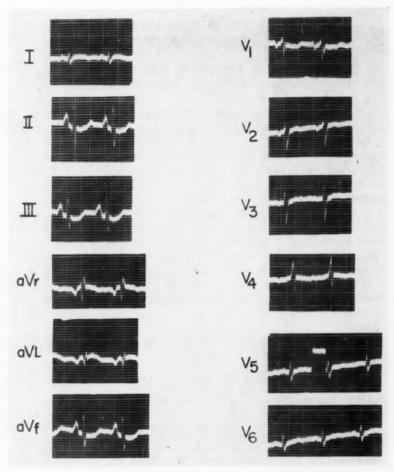


Fig. 1. Electrocardiogram of a patient with marked right and left ventricular hypertrophy at autopsy.

right ventricular enlargement and no evidence of left ventricular enlargement. The failure to recognize the markedly hypertrophied chambers may have been due either to an inability to recognize these anatomic changes, even though they are reflected in the tracings, or to the fact that the tracings failed to manifest these changes because of inadequacies of the electrocardiograph. To rationalize, one may state that the two hypertrophied ventricles "canceled the influence of each other." This may be so but, nevertheless, the anatomic changes were not recognizable with the present state of knowledge of electrocardiography and recording technics.

Electrocardiogram 2 (figure 2) was of a 58 year old white male who had had a left pneumonectomy for bronchogenic carcinoma three years prior to the development of a metastatic lesion in the right lung. The patient died shortly after the electrocardiogram was recorded. The tracing was considered to be compatible with corpulmonale. This interpretation was supported by the prominent P waves in Leads 1, 2 and 3, and the relatively prominent and slurred S waves in Leads 1, V_5 and V_6 , with relatively small slurred and notched S waves in Leads V_1 and V_2 .

with relatively small slurred and notched S waves in Leads V_1 and V_2 .

At autopsy the heart weighed 400 gm. The wall of the right ventricle was 3 mm, thick and the free wall of the left ventricle was 12 mm, thick. The pulmonary conus and the left ventricle were dilated. The right ventricle was considered to be normal.

Comment: This electrocardiogram resembles the one shown in figure 1, yet there was no right ventricular hypertrophy. Eccentric left ventricular

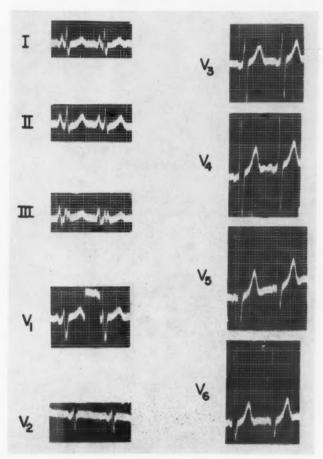


Fig. 2. Electrocardiogram of a patient with left ventricular hypertrophy at autopsy.

hypertrophy was present at autopsy but, as in the previous subject, this was not apparent from the electrocardiogram. The displacement of the heart and alterations in the extracardiac tissues as a result of the pneumonectomy may partially account for the failure of the tracing to indicate correctly the anatomic state of the myocardium. Regardless of the reasons, the heart was large, weighing 400 gm., and the electrocardiogram provided no insight into the anatomic state of the heart.

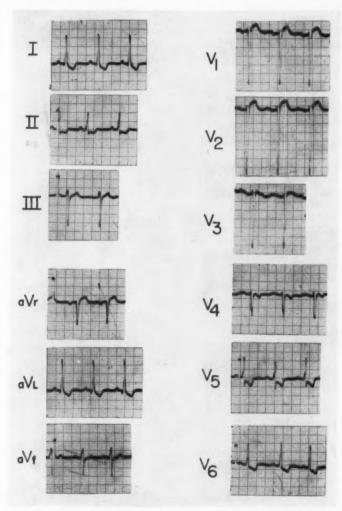


Fig. 3. Electrocardiogram of a patient with left ventricular hypertrophy at autopsy. The low R waves in the precordial leads were not due to myocardial infarction.

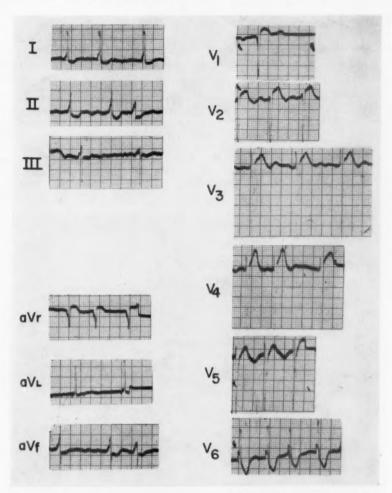


Fig. 4A. Electrocardiogram of a patient with atrial fibrillation and left ventricular hypertrophy taken upon admission to hospital.

Electrocardiogram 3 (figure 3) was of a 65 year old Negro female who had had aortic insufficiency, dyspnea and edema for several years. Six days prior to the recording she had pain in the posterior aspect of the neck, with exacerbation of dyspnea and edema. The electrocardiogram was considered to be typical of left ventricular hypertrophy. The low R waves in Leads V_1 , V_2 , V_3 and V_4 were interpreted as compatible with those found in left ventricular hypertrophy. The neck pain was considered to be referred cardiac pain, due possibly to myocardial infarction, and the low R waves in the precordial leads were interpreted as compatible with an anterior infarct.

At autopsy the heart weighed 420 gm. There were 400 c.c. of pericardial transu-

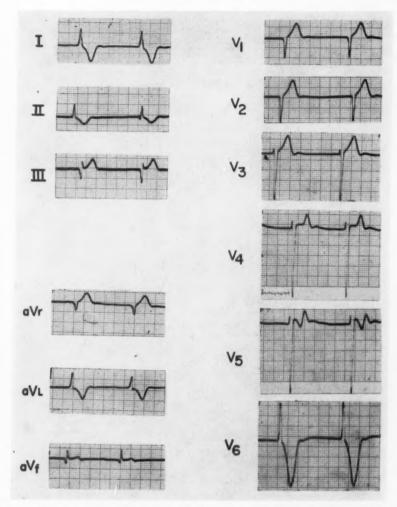


Fig. 4B. Electrocardiogram of the same patient shown in figure 4A recorded two days later and immediately after a cerebrovascular accident. Note the deep, wide T waves.

date, due to the congestive heart failure. Careful study of the heart showed no infarct. The aortic valve was insufficient.

Comment: This heart weighed about the same as those in the first two cases, but the associated electrocardiogram was typical of left ventricular hypertrophy. The heart resembled that of the second patient described, in that there was eccentric hypertrophy of the left ventricle. It is difficult to understand why the electrocardiogram of this heart was typical of left ventricle.

tricular hypertrophy when the other two were not. Although the low R waves in V₁ to V₄ were not due to an infarct in this instance, such R waves can be associated with a myocardial scar. These three electrocardiograms demonstrate aspects of the difficulties and inadequacies in the interpretation of hypertrophy of the heart from the electrocardiogram.

Electrocardiograms 4A and 4B (figures 4A, 4B) were from a 62 year old Negro female who had been admitted to the hospital with acute hypertensive encephalopathy. The patient had chronic pyelonephritis with superimposed acute pyelonephritis. Electrocardiogram 4A was considered to show atrial fibrillation with left ventricular hypertrophy. Two days later electrocardiogram 4B was recorded, which showed Q waves in Leads 2, 3 and aV₆, and wide, deep T waves such as have been previously described for cerebrovascular accidents.¹ An autopsy was not performed.

Electrocardiogram 5 (figure 5) was obtained from a 52 year old Negro female

admitted to the hospital with diabetic acidosis and a subarachnoid hemorrhage. She

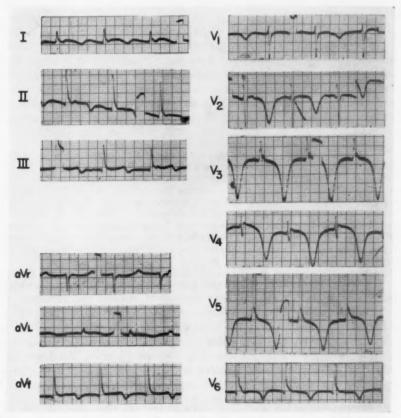


Fig. 5. Electrocardiogram of a patient with a subarachnoid hemorrhage. Note again the deep, wide T waves described for cerebrovascular accidents.

died within 24 hours of admission, and no autopsy was performed. The electrocardiogram also showed the wide and deep negative T waves described for cerebrovascular accidents.¹

Comment: The two latter patients illustrate the interesting electrocardiographic changes produced by cerebrovascular lesions. No opportunity was available to study the serum electrolytes. The first patient developed Q waves in Leads 2, 3 and aVr which suggested posterior myocardial infarction. Electrocardiogram 5 showed alterations in the time course of the terminal phases of depolarization such as have been previously described for high basal myocardial infarcts of the left ventricle.²

Recently, another patient was seen who developed this electrocardiographic pattern following a subarachnoid hemorrhage. She died two weeks later, and many small infarcts of two days' to two weeks' duration were found distributed throughout the free wall of the left ventricle, without coronary occlusion. There were no electrolyte abnormalities in this patient.

The mechanism for this electrocardiographic pattern is unknown. The nature of the changes suggests "sympathetic storms" resulting from the cerebral injury. The possibility that intense sympathetic tone is responsible for this lesion is supported by the finding of QRS changes consistent with islands of infarction or invasion block. One patient actually had many small necrotic areas of infarction without coronary occlusion. Sympathetic dysfunction is known to occur during and following cerebrovascular accidents.

Electrocardiogram 6 (figure 6) was obtained from a 29 year old white female who had had severe hypertension nine years prior to the recording. She had undergone bilateral thoracolumbar sympathectomy at that time, without success. With the use of antihypertensive agents (pentolinium tartrate (Ansolysen) and Rauwolfia serpentina (Raudixin)), and careful medical management, the blood pressure has remained within normal limits for the last three years. Although the patient is symptom-free and her retinal vessels are normal except for slight arterial narrowing, she continues to show abnormal T waves and electrocardiographic changes typical of left ventricular hypertrophy. Roentgenographic studies show moderate left ventricular enlargement.

Comment: This tracing illustrates a problem that is frequently encountered. The arterial blood pressure returned to normal and remained so for at least three years, but the T waves remain as abnormal in configuration as they were at the height of the hypertension, in spite of the fact that the other signs and symptoms have either disappeared or greatly improved. The T wave changes certainly are not due to elevated arterial blood pressure alone, but to other factors associated with the hypertensive state. Such abnormalities cause the physician difficulty when rendering a prognosis.

Electrocardiogram 7 (figure 7) was of a 55 year old white male who had had rheumatic fever at 15 years of age, and mitral stenosis with chronic congestive heart failure for many years. Acute pulmonary edema was followed by severe abdominal

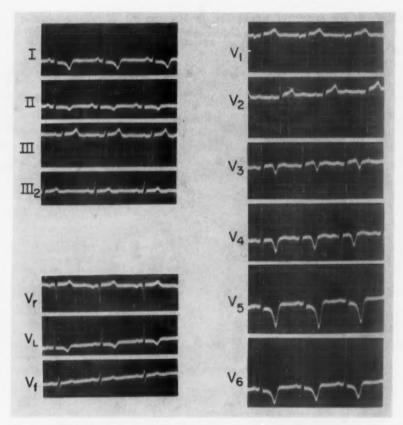


Fig. 6. Electrocardiogram of a 29 year old female who has had hypertension for nine years. For the last three years the hypertension has been well controlled. Nevertheless, the T waves have remained unchanged.

pain and sudden death. The electrocardiogram showed auricular fibrillation, right ventricular hypertrophy, and possible anteroseptal myocardial infarction.

At autopsy there was a tight mitral stenosis, right ventricular hypertrophy, marked dilatation of the right and left atria, and infarction of the small bowel. Careful search failed to uncover a myocardial infarct.

Comment: The mechanism for the absence of R waves in Leads 1, V_1 , V_2 , V_3 , V_4 and V_5 , and the presence of a Q wave in Lead 2, are difficult to explain in this patient. The R wave is often absent or small in Leads V_1 , V_2 , V_3 and V_4 in the presence of marked left ventricular hypertrophy in the absence of myocardial infarction. A similar tracing is seen in figure 3, although an R wave is present in the precordial leads. Such electrocardiographic patterns are probably related to the spatial orientation of the muscle

masses of the heart. Tracings like these cause considerable confusion to the physician whenever there is acute chest or abdominal pain and myocardial infarction is a diagnostic possibility.

Electrocardiogram 8 (figure 8) was of a 63 year old white male with diabetes mellitus, generalized arteriosclerosis, arrested pulmonary tuberculosis, dyspnea, cough, purulent sputum, diabetic retinopathy and possible bronchogenic carcinoma. The

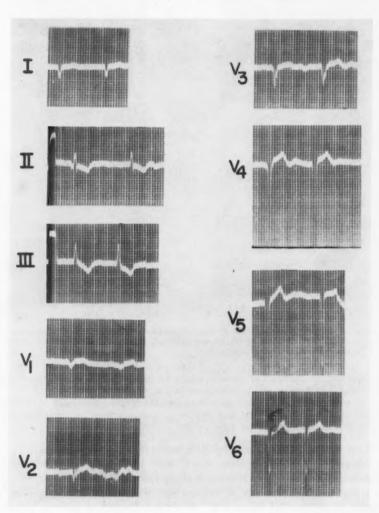


Fig. 7. Electrocardiogram of a patient with right ventricular hypertrophy. Despite the absence of R waves in Leads I and $V_{\rm r}-V_{\rm s}$ and a Q wave in Lead II, no myocardial infarction was found at autopsy.

electrocardiogram showed abnormal T waves and S-T segments which were considered to be due in part to the effects of digitalis.

At autopsy the heart weighed 480 gm. There was marked arteriosclerosis of the coronary arteries, as well as a large scar in the posterior aspect of the left ventricle. The free wall of the left ventricle was 14 mm. thick, while that of the right ventricle was 4 mm. thick.

Comment: In spite of the large posterior scar, the electrocardiogram was not considered to show myocardial infarction. The failure to detect this large scar reflects a lack of knowledge or an inadequacy in the method of recording the electrocardiogram. The mechanisms by which some lesions show characteristic changes whereas others do not remains unknown. It was shown previously in dogs ² that large, deep lesions can be produced in the myocardium without causing recognizably significant changes in the electrocardiogram.

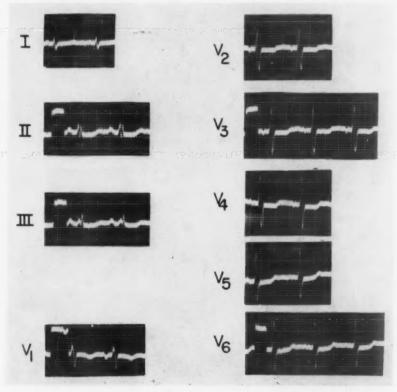


Fig. 8. Electrocardiogram of a patient with a large posterior myocardial scar which was not detected electrocardiographically.

Electrocardiogram 9 (figure 9) was of a 45 year old Negro male with amyotrophic lateral sclerosis of at least two years' duration. He was weak, emaciated and orthopneic, and had pneumonia in the right lower lobe of the lung. There was no chest pain. The blood urea nitrogen was 30 mg. per 100 ml.; serum CO₂, 19 mEq./L.; chlorides 88 mEq./L. He died five days after admission. The electrocardiogram was interpreted as showing acute anterolateral myocardial infarction.

At autopsy the heart appeared to be grossly normal. It weighed 300 gm. and showed no infarct or pericarditis. The coronary arteries were normal.

Comment: The reason for the QRS and S-T changes in this patient is unknown. Tracings such as these are frequently encountered in myocardial

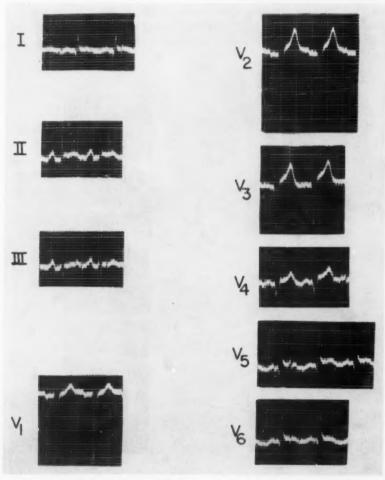


Fig. 9. Electrocardiogram of a patient whose heart was normal at autopsy.

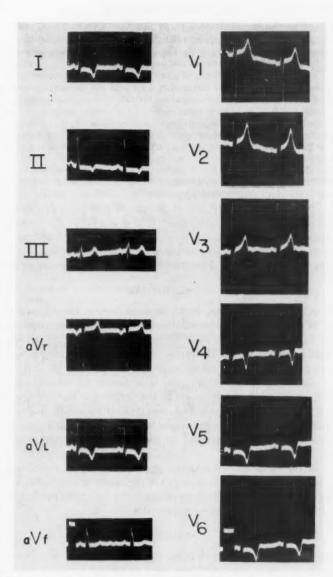


Fig. 10. Electrocardiogram of a patient with right and left ventricular hypertrophy at autopsy. There was no evidence of the right ventricular hypertrophy in the electrocardiogram.

infarction and in pericarditis; however, this patient had neither. Whether the amyotrophic lateral sclerosis and/or the changes in serum electrolytes produced the electrocardiographic configurations could not be determined. Such a tracing can be expected to cause difficulties in interpretation and management of patients.

Electrocardiogram 10 (figure 10) was of a 62 year old white male who had had hypertension with heart disease for several years. He had generalized senile arteriosclerosis and arrested pulmonary tuberculosis. The electrocardiogram was considered to show left ventricular hypertrophy.

At autopsy the heart weighed 800 gm. The wall of the left ventricle was 30 mm. thick, while that of the right ventricle was 10 mm. thick. There was marked right and left ventricular hypertrophy.

Comment: The electrocardiogram failed to display recognizable evidence of the marked right ventricular hypertrophy. The reason for this is not known. It may be considered that the electromotive force produced by the hypertrophied left ventricle overbalanced that produced by the hypertrophied right ventricle. Until the methods of recording and interpreting electrocardiograms are improved, the clinician will continue to find difficulty in recognizing right ventricular hypertrophy from the electrocardiogram.

GENERAL DISCUSSION

Without special effort, the electrocardiograms of the 10 patients presented in this report were collected from routine tracings recorded in the heart station of the New Orleans Veterans Administration Hospital and on the wards of the Charity Hospital. Such tracings illustrate only a few of the many electrocardiographic problems encountered in daily hospital practice. Since the electrocardiogram is a record of electric events, the relationship of the electrocardiogram to the pathologic state of the heart is expected to be limited. Nevertheless, every effort should be made to determine whether the electrocardiogram can be improved in both recording and interpretation in order to increase its usefulness and accuracy in clinical diagnosis.

Some of the false notions concerning the accuracy or deficiency of the electrocardiogram in clinical cardiology are the result of insufficient follow-up and autopsy correlation. Nothing makes the electrocardiographer feel humbler than the findings at the autopsy table.

SUMMARY

Electrocardiograms collected from routine records over a few days in two large hospitals in New Orleans were presented to show some of the difficulties and problems in electrocardiographic diagnosis. The hearts of most of the patients were examined at autopsy, permitting a better evaluation of the electrocardiogram. The electrocardiographic problems were discussed and the inadequacies indicated.

SUMMARIO IN INTERLINGUA

In le curso del scrutinio routinari de electrocardiogrammas specimens es incontrate que es difficile a interpretar. Si in tal casos le patiente remane disponibile usque al tempore del necropsia, le bases del difficultate deveni clar. Le presente reporto illustra certes del limitationes del interpretation electrocardiographic per correlationar datos necroptic con constatationes electrocardiographic. Es opinate que le recognition de iste limitationes per le clinico pote resultar in un melioration del diagnose electrocardiographic e per consequente in un melioration del tractamento del patiente cardiac.

Le imagine electrocardiographic e su interpretation in octo selecte casos es comparate con le stato cardiac del patiente al tempore del necropsia. In duo casos additional, le influentia de un accidente cerebro-vascular es illustrate,

Le problema de hypertrophia dextero-ventricular con basse o absente undas R es illustrate in un caso. Electrocardiogrammas de iste typo ha frequentemente essite responsabile pro le formulation de un diagnose de infarcimento antero-myocardial.

Le large, profunde undas T que es a vices incontrate in acute accidentes cerebrovascular es illustrate in duo casos,

Es presentate le electrocardiogramma de un femina hypertensive de 29 annos de etate. In despecto de un adequate regulation de su hypertension durante un periodo de tres annos, nulle melioration del undas T ha occurrite. Isto suggere que le alterationes electrocardiographic non es debite exclusivemente al hypertension del patiente. Le difficultate de formular un prognose in tal casos es obvie.

Es includite in le presentation tres casos que demonstra certes del errores que occurre in diagnoses de hypertrophia de cameras cardiac super le base del examine de electrocardiogrammas.

Proque le electrocardiogramma es un reflexion de eventos electric, su relation al stato pathologic del corde es limitate. Meliorationes de tanto le registration como etiam le interpretation del electrocardiogramma es necessari pro meliorar le accuratia del electrocardiogramma in le diagnose clinic.

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OBSERVATIONS ON THE EFFECTS OF ALKYLAT-ING AGENTS IN HUMAN NEOPLASTIC DISEASE * †

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DURING the last few years, evaluation at the clinical level of the growthinhibiting properties of various chemotherapeutic agents has demonstrated the lack of an easily definable pattern with which to predict what degree of growth-inhibitory action may be shown by any given compound under investigation among the broad spectrum of the neoplastic diseases. It is known that tissues with rapid rates of growth are more susceptible to injury by chemical compounds than are those with relatively slow rates of growth, but this generalization applies to normal tissues as readily as it does to malignant tissues. For example, the hemopoietic tissues and the epithelial lining of the alimentary tract are far more susceptible to the growth-inhibiting properties of the folic acid antagonists than is muscle or bone.

Restriction of neoplastic cell growth by certain chemotherapeutic agents has been particularly effective in malignant diseases of the hemopoietic system (notably the leukemias and the malignant lymphomas), but an increasing amount of evidence has been accumulated to show that the growth of certain disseminated, neoplastic "solid" tumors may be adversely affected by chemical compounds also. In our experience, certain polyfunctional alkylating agents have proved to be useful clinically in the palliative treatment of a limited number of disseminated solid tumors, as well as in the leukemias and malignant lymphomas, when other methods of treatment are not practicable. It is the purpose of this paper to demonstrate the variability of the growth-inhibiting properties of various alkylating agents, and to emphasize the importance of testing each new agent against a wide variety of neoplasms, not only at different dosage levels but also by different modalities of administration.

Table 1 lists the neoplastic diseases in the two categories, i.e., "hemopoietic" and "solid" tumor types, and the chemical compounds that may affect them. This table is based on our own experience, and is not meant to be an all-inclusive summary of the work in this field.

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TABLE 1

| | Type of Cancer Affected | |
|--|--|---|
| | Hemopoietic Diseases | "Solid" Tumors |
| Alkylating Agents A. Nitrogen Mustards I. HN₁ methyl-bis(β-chloroethyl)-amine HCl; mechlorethamine; Mustargen. | Malignant lymphomas Mycosis fungoides Chronic lymphocytic leukemia | Bronchogenic carcinoma |
| C.B. 1348 p-(di-2-chloroethylamino)- phenylbutyric acid; chlor- ambucil; Leukeran. | Giant follicle lymphoma Lymphosarcoma Hodgkin's disease Mycosis fungoides Chronic lymphocytic leukemia | 1. Undifferentiated carcinoma |
| 3. C.B. 3025 p-di-(2 chloroethyl)-amino- L-phenylalanine | | 1. Malignant melanoma |
| B. Ethylenimines 1. TEM 2, 4, 6-triethylenimino-S-triazine; triethylene melamine | Lymphosarcoma Hodgkin's disease Giant follicle lymphoma Chronic lymphocytic leukemia Chronic granulocytic leukemia | Ovarian carcinoma Carcinoma of the breast with pleural effusion Retinoblastoma* |
| Thio-Tepa N.N'.N"-triethylene thio- phosphoramide | Chronic lymphocytic leukemia Lymphosarcoma | Ovarian carcinoma Undifferentiated carcinoma, uterine corpus Transitional cell carcinoma, urinary bladder Carcinoma of the breast with pleural effusion |
| 3. E-39 2,5-di-propyloxy-3,6-di- ethyleniminobenzoquinone | Malignant lymphoma Chronic leukemia | Undifferentiated carcinoma of the lung, stomach, colon ovary |
| C. Sulfonic Acid Esters 1. Busulfan 1.4-dimethane-sulfonyl- oxybutane; Myleran. | Chronic granulocytic leukemia Acute stem cell leukemia | |

* Combined with irradiation.

POLYFUNCTIONAL ALKYLATING AGENTS

Nitrogen Mustards

Mechlorethamine: The aliphatic nitrogen mustard compound, mechlorethamine (methyl-bis (β-chloroethyl)amine HCl; HN₂) has been used widely in clinical medicine since the end of World War II. In the body fluids it rapidly undergoes chemical transformation, combining with reactive compounds, and hence is no longer present in active form after a few minutes. Because it is a powerful local vesicant, it should be given by parenteral routes of administration, preferably in either of two ways: (1) intravenous injection which is by far the most common method employed; and (2) intracavitary injection for attempted control of malignant effusion. The intraarterial administration of mechlorethamine, a procedure distinctly more hazardous than the intravenous or intracavitary methods of administering the drug, will not be discussed in this paper. While the pharmacologic effects of HN₂ administration are produced in an unusually rapid manner, the remissions so induced usually are of short duration, varying from a few weeks to two or three months in malignant lymphoma. In superior yena

caval obstruction secondary to bronchogenic carcinoma, relief of obstructive symptoms not infrequently can be obtained from the intravenous administration of HN₂, but relief is transient, seldom lasting more than two or three weeks. Toxic side-effects are characterized by nausea and vomiting, thrombophlebitis, and mild to severe suppression of hemopoiesis.

Chlorambucil: P-(di-2-chloroethylamino)-phenylbutyric acid (C.B. 1348; chlorambucil; Leukeran) is an aromatic nitrogen mustard that was synthesized by Everett et al. in 1953. It is a water-soluble compound that is readily absorbed from the gastrointestinal tract, and hence the drug may be given by mouth. In contrast to mechlorethamine, the action of C.B. 1348 is delayed, so that measurable clinical responses often become manifest three to six or more weeks after institution of treatment. The principal toxic manifestation of C.B. 1348 is suppression of hemopoiesis, but this usually develops only after many weeks of continuous administration of the drug, and may be minimized or avoided by intermittent administration at moderate dosage levels. Anorexia and nausea are rare, and vomiting seldom occurs.

Because of the immediate action of mechlorethamine and the delayed response with chlorambucil, we have employed both of these compounds in the treatment of widely disseminated "solid" neoplasms. Mechlorethamine in a standard dose of 0.4 mg./Kg. of body weight has been given intravenously first, and the administration of chlorambucil in a dosage of 0.2 to 0.3 mg./Kg./day was begun from two to three weeks later in cases where suppression of hemopoiesis did not occur after the injection of mechlorethamine. Whenever HN₂-induced suppression of hemopoiesis was observed, the administration of chlorambucil was withheld until normal bone marrow function was restored.

L-phenylalanine Mustard: A compound closely related structurally to Leukeran, p-di(2 chloroethyl)-amino-L-phenylalanine (C.B. 3025, L-phenylalanine mustard) was first synthesized by Bergel and Stock.³ Since melanin-producing enzymes of melanocytes were thought to utilize phenylalanine, Luck ⁴ tested L-phenylalanine mustard on the Harding-Passay mouse melanoma and reported antitumor activity. Subsequently, this compound was subjected to clinical trial. It was supplied in the form of 2.0 mg. tablets for oral administration. Eight to 16.0 mg. a day were given over a period of three to four weeks, or until signs of suppression of hemopoiesis occurred. Among 12 patients with metastatic melanoma in our series who were treated in this manner, two showed objective evidence of regression of tumor for limited periods of time (four months in one case, nine months in the other).

Ethylenimines

Triethylene Melamine: While 2,4,6-triethylenimino-S-triazine (TEM) has been found to be particularly useful in the treatment of the chronic leukemias and the malignant lymphomas, it has been found also to have limited usefulness in the treatment of ovarian carcinomatosis.⁵⁻⁷ It is readily ab-

sorbed from the gastrointestinal tract, and therefore may be given by mouth. It also may be administered parenterally, or instilled into serous cavities. The re-accumulation of pleural or ascitic effusions secondary to carcinoma of the ovary or of the breast, or to a malignant lymphoma, not infrequently may be delayed for weeks or months following withdrawal of fluid from the serous cavity and the instillation of crystalline TEM dissolved in 20 to 30 ml. of physiologic saline solution. The dose of TEM for intracavitary instillation varies from 2.5 to 5.0 mg, for effusions secondary to lymphomatous disease, and from 7.5 to 10.0 mg, for effusions due to carcinoma.

With oral administration, TEM, together with 1 to 2 gm. of sodium bicarbonate and water, is given on an empty stomach one hour or more before breakfast at intervals of from seven to 10 days. Since the principal toxic action of the drug is suppression of hemopoiesis, blood counts should be performed prior to each re-administration of the agent. Treatment should be discontinued promptly if leukopenia, thrombocytopenia or anemia develops. Dosage schedules vary widely-from 2.5 to 5.0 mg. per weekly dose in chronic lymphocytic leukemia and malignant lymphoma, to 7.5 to 10.0 mg. in ovarian carcinomatosis, and to 10.0 to 15.0 mg. in chronic granulocytic leukemia.

Thio-Tepa: N,N',N"-triethylene thiophosphoramide (Thio-Tepa) appears to be unique among the ethylenimine compounds in having a wider range of activity among the neoplastic solid tumors and the malignant hemopoietic diseases than do other alkylating agents.⁷⁻⁸ It may be administered orally or parenterally, instilled into serous cavities, or injected directly into It is not irritative to normal tissues when introduced into a serous cavity or into muscle, as judged by the lack of a local inflammatory reaction, and it does not delay wound healing when introduced into the peritoneal cavity during or immediately after surgical procedures. Its principal toxic action is suppression of hemopoiesis.

The total amount of Thio-Tepa required to produce either objective evidence of a clinical response or suppression of hemopoiesis varies greatly from one patient to another. With intravenous administration, the majority of patients in our series tolerated a total dose of from 1.0 to 2.0 mg./Kg. of body weight if the drug was given in small divided doses every second or third day over a period of two to four weeks. During the initial period of therapy, blood counts should be performed prior to each injection of the drug, and treatment should be discontinued if leukopenia, thrombocytopenia

or a progressive fall in hematocrit or hemoglobin levels is noted.

With intracavitary administration, doses of from 30 to 40 mg, of Thio-Tepa, dissolved in 30 ml. of physiologic saline solution, usually are well tolerated. Before each instillation of the drug, the cavity into which it is to be introduced should be tapped as dry as possible, and, following the instillation, the patient should be turned at intervals of from five to 10 minutes for an hour or more to facilitate widespread distribution within the cavity and thereby to provide contact with the entire serosal surface. For intratumor injection, doses varying from 10 to 60 mg., dissolved in 5.0 to 20.0 ml. of saline solution, have been employed. The size of the dose and the volume of fluid in which it is given must be gauged by the size of the tumor to be injected. If the tumor to be injected appears to be vascular, doses in excess of 40.0 mg. may be followed by suppression of hemopoiesis, due to

rapid absorption of the compound into the blood stream.

E-39: One of the newer ethylenimines, 2,5,-di-propyloxy-3,6-di-ethyleniminobenzoquinone (E-39), introduced by Domagk in 1956,9-11 has been studied by us for the last 18 months. It can be given either intravenously or orally. It is stable in the form of a dry powder, and hence is supplied in the dry state in sterile vials, each containing 10.0 mg. of the drug. Since it is soluble in absolute alcohol but not in water, each 10.0 mg. lot is first dissolved in 1.0 ml. of absolute alcohol and then diluted further with sterile normal saline solution before being given to the patient. With intravenous administration, 20.0 to 30.0 mg. of the drug are given daily until a mild degree of leukopenia is observed, then the size of the daily dose is decreased or the frequency of the injections is diminished. The total dose for a single course of administration varies from 400 to 800 mg. or more. Toxic reactions are characterized by suppression of hemopoiesis and thrombophlebitis. In the opinion of the writer, the latter is a serious complication because it occurs in all cases, and even though each individual dose is given in 250 to 500 ml, of normal saline solution, there is sufficient irritation of the vein that gradual fibrosis with a resultant obliteration of the lumen occurs. Hence, the subsequent administration of intravenous infusions and blood transfusions becomes increasingly difficult.

Busulfan: 1-4-dimethane-sulfonyloxybutane (Myleran), a sulfonic acid ester, was shown by Haddow and Timmis ¹² to inhibit animal tumors and granulocyte formation in animals. Subsequent studies by Galton ¹³ and others revealed that this agent is extremely useful in the treatment of chronic granulocytic leukemia in man. It also has a limited usefulness in the treatment of the acute terminal phase of chronic granulocytic leukemia, but is ineffective in the treatment of disseminated "solid" tumors. Since Myleran is readily absorbed from the gastrointestinal tract, it is effective after oral administration. In patients with high leukocyte counts, 6.0 to 10.0 mg. are administered by mouth daily in divided doses until a significant fall in the leukocyte count has occurred; then the dose is reduced gradually to 4.0 or 2.0 mg. daily as the leukocyte count approaches a normal level. Toxicity is characterized predominantly by suppression of granulocytopoiesis.

DISEASES AFFECTED BY ALKYLATING AGENTS

The Leukemias

Chronic Granulocytic Leukemia: Control of chronic granulocytic leukemia may be effected by the alkylating agents, busulfan (Myleran) and

triethylene melamine (TEM), as well as by the colchicine analogue, demecolcin (Colcemid), and by the purine antagonist, 6-mercaptopurine (6-M.P., Purinethol).

In our hands, Myleran has proved to be the most satisfactory agent because of ease of administration, the absence of untoward side-effects, and the smooth course of the response. In patients with initial leukocyte counts in excess of 100,000 cells per cubic millimeter, 6.0 to 8.0 mg. are administered by mouth daily until the leukocyte count approaches a level of 25,000 to 30,000 cells per cubic millimeter; then the dose is reduced to 4.0 mg. or less a day until the leukocyte count reaches a normal value. Concomitant with the fall in the leukocyte count, clinical improvement almost invariably occurs, as manifested by reduction in the size of the spleen, and often of the liver, improvement or disappearance of anemia, a return of strength to normal, and improved appetite, followed by gain in weight. In most cases the number of immature granulocytes in the circulating blood is markedly reduced, and in some instances, immature cells disappear entirely from the blood stream for varying periods of time. Once a remission has been produced the administration of Myleran should be discontinued, because in a limited number of patients prolonged remissions which do not require maintenance therapy may be observed. In one of our patients a Myleraninduced remission lasted two years before relapse occurred and a second course of Myleran therapy was given. In most patients, however, Myleraninduced remissions are short, rarely lasting more than two to four weeks, and in these, maintenance therapy is necessary for effective control of the disease. This usually can be accomplished by the administration of 1.0 to 3.0 mg. of the drug daily.

While TEM will produce good initial hematologic and clinical responses in chronic granulocytic leukemia, it is less satisfactory than Myleran for maintenance therapy. Since the maximal suppression of hemopoiesis occurs from five to seven days after administration of the compound, we prefer to give TEM in a single dose once each week, or in divided doses on two consecutive days once a week. In patients with leukocyte counts in excess of 100,000 cells per cubic millimeter, 10.0 to 15.0 mg, of TEM are administered orally, together with 2.0 gm. of sodium bicarbonate and water, at intervals of one week until the leukocyte count falls below 50,000 cells per cubic millimeter; then the dose is reduced to 7.5 or 5.0 mg. per week until the leukocyte count approaches a normal value. Once a normal level has been attained, the administration of the drug is discontinued until the leukocyte count again rises above normal values. Since the duration of TEM-induced remissions varies from two or three weeks to several months, moderately severe degrees of relapse may occur before the relapse is discovered unless blood examinations are made at frequent intervals.

Chronic Lymphocytic Leukemia: In the asymptomatic stage of chronic lymphocytic leukemia, conservative management is advisable because the

disease may remain inactive for years. We followed three patients for five, eight and 16 years, respectively, before treatment was required. The indications for treatment are: progressive enlargement of lymph nodes, visceral involvement (hepatosplenomegaly, etc.), and the development of anemia (myelophthisic or hemolytic). Prolonged hematologic and clinical remissions can be obtained with TEM or with Leukeran. When TEM is employed, a small test dose (2.5 mg.) should be given first, to determine the degree of sensitivity to the drug, before embarking on a specific program of treatment. The authors have witnessed a fall in the leukocyte count from 103,000 cells per cubic millimeter to 5,000 cells per cubic millimeter over a period of eight days in a patient who received a single oral dose of 5.0 mg. of TEM. In less sensitive patients, doses of from 5.0 to 7.5 mg. should be given weekly until a remission has been induced, then administration of the drug should be discontinued until relapse occurs. We have found TEM to be particularly useful in the treatment of patients with a severe anemia secondary to marked lymphocytic infiltration in the bone marrow. The pronounced lymphocytolytic action of the compound may produce a sufficient degree of destruction of lymphocytes in the marrow that erythropoiesis (and the anemia) are decidedly improved and, in some instances, may be restored to normal.

Leukeran is also an effective and useful drug in the treatment of this disease, but occasional cases respond poorly or not at all. The compound is administered orally in a dosage of from 0.2 to 0.3 mg. per kilogram of body weight per day until the leukocyte count falls below 20,000–25,000 cells per cubic millimeter; then the dose is reduced to 0.1 mg./Kg./day or less. As a rule, treatment should be discontinued when the leukocyte count reaches normal levels, but in patients with massive adenopathy the continued administration of small doses of the drug may result in further regression in the size of lymph nodes without producing leukopenia. A longer period of time is required to produce optimal therapeutic results with Leukeran than with TEM, but Leukeran is well tolerated and is a safer drug to use.

Malignant Lymphoma

X-ray therapy is the preferred method of treatment for early, localized or moderately advanced stages of lymphomatous diseases. However, alkylating agents, used alone or in combination with irradiation, are useful in the treatment of patients with widely disseminated disease. Not only will they cause regression of enlarged lymph nodes, spleen and liver, but frequently they also alleviate the systemic symptoms of fever, hyperhidrosis, anorexia and pruritus.

The choice of what agent to employ is based in part on the experience and the judgment of the physician treating the patient, and in part on the type of lymphoma to be treated. We prefer to use mechlorethamine (HN₂) alone, or in combination with irradiation, on far advanced Hodgkin's dis-

ease and in reticulum cell sarcoma. In acute cases of Hodgkin's disease and of lymphosarcoma, good remissions can sometimes be obtained by the administration first of HN_2 , followed by a course of Leukeran therapy, but in occasional cases Leukeran, used alone, may induce prolonged remissions (case 1). TEM or Leukeran can often be employed advantageously in the treatment of giant follicular lymphoma and the chronic form of lymphosarcoma. In our experience, Leukeran is less likely than is TEM to cause serious suppression of hemopoiesis when either drug is administered over a prolonged period of time.

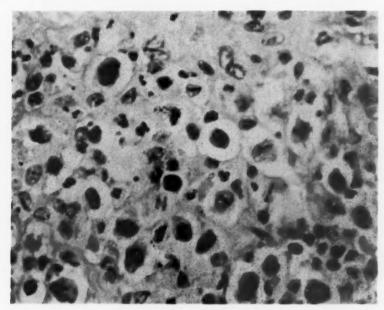


Fig. 1. Case 1. Photomicrograph of left supraclavicular lymph node, showing the granulomatous form of Hodgkin's disease. × 400.

CASE REPORTS

Case 1. E. J., female, aged 12 years.

April, 1954: A mass in left supraclavicular region was observed. Biopsy of a lymph node revealed Hodgkin's disease (figure 1).

May 3 to 26, 1954: Treated by irradiation, 2,400 r in air being delivered to a 15 by 15 cm. portal.

May 27 and 29, 1954: Received two injections of HN2, 6.0 mg. each.

June to September, 1954: Clinically well; then enlarged left cervical nodes and a subcutaneous mass below the left clavicle were noted.

September to October, 1954: Received 2,050 r in air to left cervical region, and 900 r in air to left infraclavicular mass.

October to November, 1954: Clinically well.

December, 1954: Recurrence of adenopathy and onset of fever, malaise, anorexia and weight loss.

January 14, 1955: Examination revealed marked enlargement of lymph nodes in both axillae and supraclavicular regions, a 7.0 by 5.5 cm. mass in the chest wall below the left clavicle, fever to 104° F., and evidence of weight loss. X-ray film of the chest revealed enlargement of mediastinal and hilar lymph nodes, and extensive involvement of the parenchyma of both lungs (figure 2).

January 14 to March 8, 1955: A total dose of 537 mg. of Leukeran was administered over a period of approximately seven weeks. Clinical improvement was

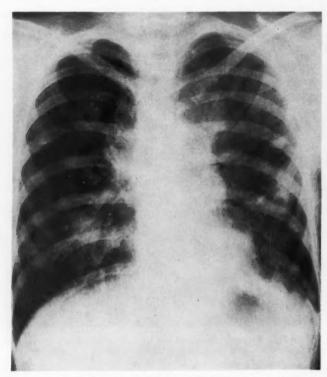


Fig. 2. Case 1. Chest film, taken on January 27, 1955, at the beginning of treatment with Leukeran, revealed enlargement of hilar and mediastinal lymph nodes and extensive involvement of the parenchyma of both lungs.

striking, as manifested by disappearance of fever, return of appetite, gain in weight and strength, marked regression of adenopathy, and clearing of the lesions in the parenchyma of the lungs (figure 3).

March, 1955, to October, 1956: Treated intermittently with Leukeran therapy until October, 1956, when treatment was discontinued because of the development of a leukopenia of 2,800 cells per cubic millimeter. This was followed by rapid and progressive enlargement of hilar lymph nodes and parenchymal lesions. Irradiation was administered elsewhere, without significant effect. Patient died on December 11, 1956.

Case Summary: Exceedingly good control with intermittent Leukeran therapy was obtained in this patient, who had far-advanced Hodgkin's disease when treatment was begun. A total dose of 3.46 gm. was administered over a period of 21 months without causing serious injury to hemopoiesis. During most of this period the patient led a normal, active life despite roentgenographic evidence of residual disease in the lungs.

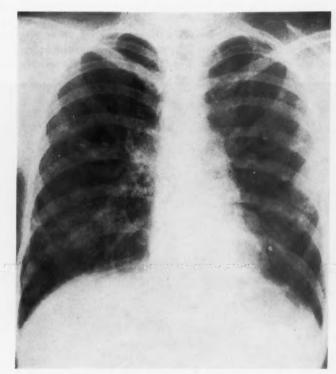


Fig. 3. Case 1. Chest film, taken on March 8, 1955, after the patient had received a total dose of 537 mg. of Leukeran, disclosed marked regression of hilar and mediastinal adenopathy and clearing of the parenchymal lesions. These changes were accompanied by striking improvement in the general condition of the patient. No other form of therapy was employed.

CARCINOMA

Well differentiated carcinomas of the gastrointestinal tract and of the lung, and carcinoma of the pancreas and of the kidney, are particularly resistant to treatment with alkylating agents. However, varying degrees of suppression of tumor cell growth may sometimes be observed following the use of alkylating agents in undifferentiated carcinomas of the lung, stomach and colon, in adenocarcinoma of the breast, in serous cystadenocarcinoma of the ovary, and in transitional cell carcinoma of the urinary bladder.

Carcinoma of the Lung: Objective evidence of tumor regression can be obtained with HN_2 in approximately 30% of patients having inoperable carcinoma of the lung, but the response is usually of short duration, varying from two to six or eight weeks. The administration of HN_2 followed by local irradiation of the lung tumor has been advocated by some investigators, but it is difficult to determine whether the response to combined therapy is superior to irradiation used alone. We have seen a prolonged response in one patient with widespread pulmonary metastases from an undifferentiated carcinoma, primary site unknown but thought to arise in the lung, who was treated first with HN_2 , then with Leukeran, and finally with combined

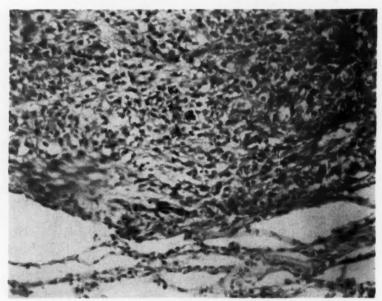


Fig. 4. Case 2. Photomicrograph of the lesion resected from the left lung in 1953. The pathologic report was that of an undifferentiated carcinoma, primary site undetermined. × 120.

Leukeran and x-ray therapy (case 2). E-39 will also cause objective improvement in lung cancer, three of 10 patients in our series having benefited for periods up to four and one-half months. One patient with a superior vena cava syndrome was relieved of obstructive symptoms for a period of four months while under treatment with this compound.

Case 2. K. W., female, aged 56 years.

1951: Hysterectomy for fibromyomata of the uterus.

1953: Routine chest film revealed a solitary "coin" lesion in the lower lobe of the left lung. Lesion resected. Pathologic report: undifferentiated carcinoma (figure 4), probably metastatic; primary site undetermined.

April, 1955: Onset of fatigue and exertional dyspnea.

June, 1955: Chest film revealed multiple metastatic lesions in both lungs (figure 5).

July 18, 1955: Intravenous administration of 28.0 mg. of HN_2 (Mustargen). This was followed by a pancytopenia, lasting approximately six weeks.

September 1, 1955, to July 10, 1956: Treated with Leukeran, administered orally (daily); dose varied from 16.0 to 4.0 mg.; total dose in 10 plus months, 1,766 mg. July 5, 1956: Chest film revealed disappearance of several small lesions and a marked reduction in size of most of the larger masses, except for one nodule in the

right lower lobe (figure 6).

October, 1956, to March, 1958: Treated with intermittent Leukeran therapy plus two courses of irradiation with the 6 Mey linear accelerator to nodular lesions in

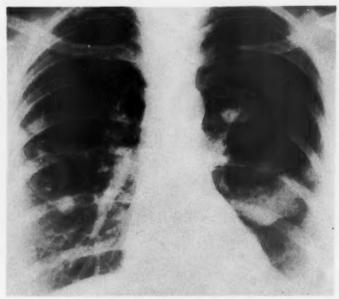


Fig. 5. Case 2. Chest film, taken on June 10, 1955, prior to the institution of treatment, revealed multiple metastatic lesions in both lungs.

both lungs. Total dose of Leukeran administered over a period of 30 months, 2,918 mg. Hemogram on April 17, 1958: hemoglobin, 9.4 gm.; red blood cells, 3,020,000; white blood cells, 4,500; neutrophils 62%; platelets, adequate on blood smear.

May, 1958: Onset of pain in left hip. X-ray films revealed metastasis in left ischium. Progressive downhill course thereafter. Died on November 20, 1958.

Case Summary: Remarkable regression of metastatic lesions in the parenchyma of both lungs was observed in this patient following a single intravenous injection of HN_2 and the oral administration of Leukeran over a period of $10\frac{1}{2}$ months. Thereafter, the pulmonary lesions were controlled with intermittent Leukeran therapy and irradiation until evidence of extrapulmonary metastasis was noted almost three years after the institution of therapy. During the greater part of this three-year period the patient was asymptomatic and led a normal, active life.

Carcinoma of the Gastrointestinal Tract: In our series of cases, E-39 has caused objective evidence of tumor regression in one of four patients with carcinoma of the colon, and in two of four patients with carcinoma of the stomach, but the periods of improvement have been short, lasting not more than four months. In one patient with carcinoma of the stomach, the administration of E-39 was followed by regression in the size of a tumor mass (Virchow's lymph node) in the left supraclavicular area (from measurements of 3.0 by 2.5 cm. before treatment to 1.0 by 0.5 cm. during treatment). It is of interest that rapid growth of tumor occurred in two of the three

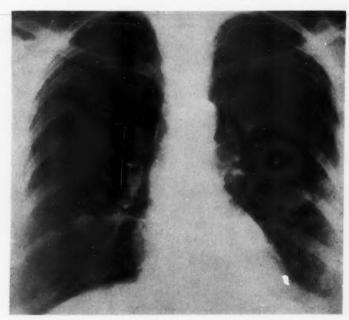


Fig. 6. Case 2. Chest film, taken on July 5, 1956, disclosed a significant degree of regression of most of the larger masses and disappearance of several small lesions. Treatment during this period consisted of a single intravenous injection of HN₂, followed by the intermittent oral administration of Leukeran.

patients in whom an initial response was observed when the administration of E-39 was discontinued because of the development of leukopenia, anemia or thrombocytopenia.

Carcinoma of the Ovary: Thio-Tepa and TEM are useful agents in the treatment of ovarian carcinomatosis and, in our experience, are superior to E-39. Re-accumulation of peritoneal or pleural effusions can be delayed or prevented for weeks or even months by the intracavitary instillation of either agent, followed by a prolonged course of intravenous Thio-Tepa therapy (case 3). For patients with abdominal carcinomatosis without

ascites, objective improvement has been noted on administering Thio-Tepa intravenously for prolonged periods. In our series of 28 cases, serous cystadenocarcinoma has proved to be far more responsive to chemotherapy than is the pseudomucinous type of ovarian tumor.

Case 3. D. G., female, aged 25 years.

December, 1957: Onset of recurrent low abdominal and pelvic pain. January, 1958: Pelvic examination elsewhere said to be negative.

March, 1958: Pelvic examination: left ovarian tumor found.

March 17, 1958: Exploratory laparotomy performed. Bilateral ovarian masses (8.0 to 10.0 cm. in diameter) were found, and a panhysterectomy was performed. Residual tumor was known to have been left in the pelvis. Pathologic report: papillary cystadenocarcinoma (figure 7).

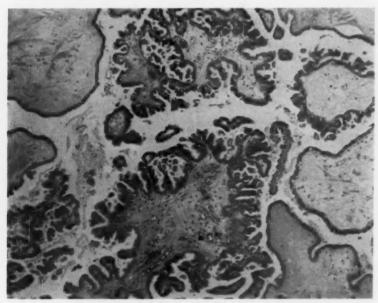


Fig. 7. Case 3. Photomicrograph showing papillary or serous cystadenocarcinoma of the ovary. × 80.

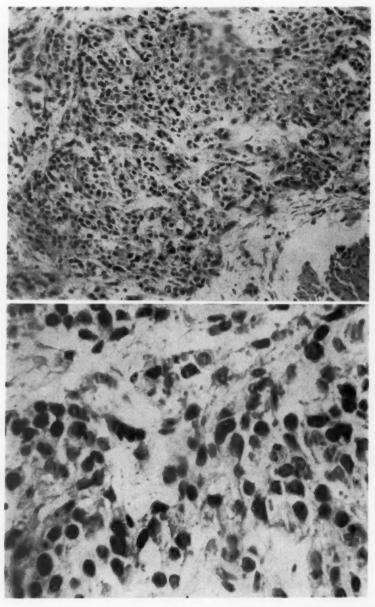
March 24 to April 29, 1958: Received irradiation with the 6 Mev linear accelerator, 5,000 rads being delivered to the midpelvis.

June, 1958: Enlargement of abdomen noted.

June 23, 1958: Paracentesis, with removal of 4,700 ml. of serous fluid. Papanicolaou's smears positive for malignant cells. Ten milligrams of TEM instilled into the peritoneal cavity.

July 1 to 7, 1958: Twenty milligrams of Thio-Tepa administered intravenously in divided doses; further treatment discontinued because of leukopenia and anemia. October, 1958, to April, 1959; Following the return of blood counts to normal,

the intravenous administration of Thio-Tepa at monthly intervals was resumed. Patient entirely well. Abdominal and pelvic examinations negative.



Figs. 8 (above) and 9 (below). Case 4. Photomicrographs of specimen removed from the urinary bladder in October, 1955. The pathologic report was that of an infiltrating transitional cell carcinoma, grade III. \times 130 and \times 460.

Case Summary: The intraperitoneal instillation of TEM, followed by the intravenous administration of Thio-Tepa, seems to have prevented the re-accumulation of ascites for a period of slightly more than 10 months in a patient with ovarian carcinomatosis.

Carcinoma of the Urinary Bladder: In a series of 12 patients with recurrent, far advanced transitional cell carcinoma of the bladder, Reynolds et al. 4 observed marked objective improvement in three of 11 patients in whom Thio-Tepa was injected directly into tumor, and in one patient with metastases to the lymph nodes and the lungs. Case summaries for two of these patients are as follows:

Case 4. L. B., male, aged 65 years.

1952: Transurethral resection for benign prostatic hypertrophy.

September, 1955: Onset of hematuria.

October 3, 1955: Cystoscopy: Large papillary tumor of right bladder wall with extravesical extension noted. Biopsy performed. Pathologic report: infiltrating transitional cell carcinoma of urinary bladder, grade 3 (figures 8 and 9).

October 5 to November 4, 1955: X-ray therapy: 4,046 r estimated tumor dose delivered through six portals.

January 23, 1956: Bimanual examination revealed a large tumor, approximately 7.0 cm. in diameter, on the right side of the pelvis. Cystoscopy: biopsy repeated. Pathologic report: transitional cell carcinoma, grade 3. Through a long, flexible needle, introduced into the urinary bladder through the cystoscope, 40.0 mg, of Thio-Tepa and 600 units of hyaluronidase in a total volume of 8.0 ml. of isotonic saline solution were injected by means of multiple punctures directly into the tumor. Subsequent treatment and the results observed are shown in table 2.

Case Summary: Serial intratumor injections of Thio-Tepa, with hyaluronidase used simultaneously as a spreading agent, have resulted in what appears to be complete disappearance of an infiltrative type of carcinoma of the urinary bladder over a period of approximately three years. Objective signs of recurrence have not as yet reappeared.

TABLE 2

| | D | osage | Volume of Solu- | | | |
|---------|-----------------------|------------------------------|----------------------------|---|--|----------------------------|
| Date | Thio- Tepa, mg. | Hyaluro- nidase, units | tion In- jected, ml. | Cystoscopic Examination | Biopsy Report | Bimanual Examination |
| 1/23/56 | 40 | 600 | 8.0 | Tumor, r. bladder wall | Cancer, grade | Tumor, 7.0 cm. diameter |
| 2/1/56 | 40 | 600 | 8.0 | Tumor markedly re- duced in size | | Tumor, 2.0 cm. diameter |
| 3/12/56 | 30 | 400 | 20.0 | No tumor visualized | _ | Tumor not palpable |
| 5/28/56 | 60 | 1,500 | 12.0 | Small papillary tumor adjacent to r. ureter | Cancer, grade | |
| 9/24/56 | _ | - | _ | Slough in r. bladder wall | Cystitis cystica, chronic inflam, | Negative |
| 4/23/57 | | | | Residual scar tissue | _ | Negative |
| 5/12/58 | | _ | | Residual scar tissue | | Negative |

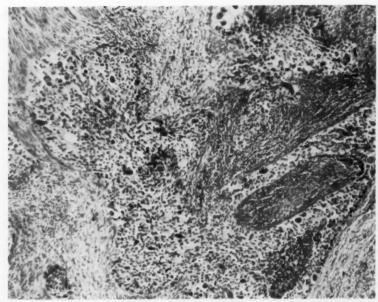


Fig. 10. Case 5. Photomicrograph of the infiltrating transitional cell carcinoma of the urinary bladder, resected in October, 1957. \times 80.



Fig. 11. Case 5. Photomicrograph of left inguinal lymph node, excised March 28, 1958, showing metastatic anaplastic transitional cell carcinoma. \times 80.

Case 5. B. M., female, aged 67 years.

March, 1955, and September, 1955: Cystoscopic examinations and fulguration of bladder tumor.

June, 1957: Recurrence of hematuria, but patient did not seek medical advice until late September, 1957.

October, 1957: Partial cystectomy for recurrent bladder tumor. Pathologic report: anaplastic, infiltrating transitional cell carcinoma of the urinary bladder (figure 10).

March, 1958: A mass in left inguinal region noted and another in the anterior wall of the vagina.

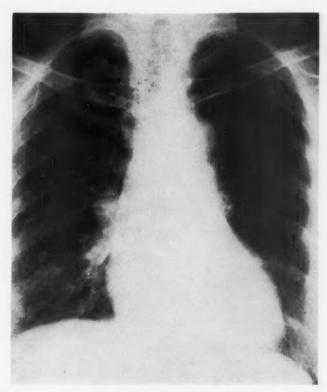


Fig. 12. Case 5. Chest film, taken on April 1, 1958, revealed right hilar adenopathy and multiple small metastatic lesions throughout both lung fields.

March 28, 1958: Biopsy of left inguinal lymph node and excision of mass in vaginal wall. Pathologic report: recurrent anaplastic transitional cell carcinoma (figure 11, lymph node).

April 1, 1958: Chest film revealed right hilar adenopathy and multiple small nodular infiltrations in the parenchyma of both lungs, interpreted as being due to metastases (figure 12).

April 10, 1958, to January 5, 1959: Serial intravenous injections of Thio-Tepa administered (total dose, 250.0 mg.).

September 22, 1958: Chest film revealed marked decrease in size of the right hilar adenopathy and virtual disappearance of the parenchymal lesions (figure 13).

April, 1959: Patient clinically well. Left inguinal lymph nodes no longer palpable. Hemogram normal.

Case Summary: A patient with metastases to the parenchyma of both lungs and to the right hilar and left inguinal lymph nodes, originating from a recurrent anaplastic transitional cell carcinoma of the urinary bladder, has been free of clinical evidence of the disease for a period approaching one year following a sustained course of treatment with Thio-Tepa, administered intravenously.

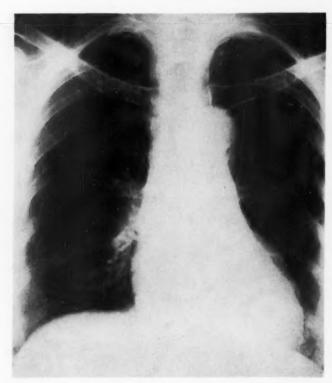


Fig. 13. Case 5. Chest film, taken on September 19, 1958, disclosed a decrease in size of the right hilar lymph nodes and a significant degree of regression of the parenchymal lesions following treatment with Thio-Tepa.

Malignant Melanoma: Tepa (triethylene phosphoramide), Thio-Tepa and L-phenylalanine mustard have been used in the treatment of malignant melanoma. Objective evidence of improvement may occasionally be observed. We have seen objective improvement in one of 36 patients treated with Thio-Tepa, and in two of 12 patients treated with L-phenylalanine

mustard. The case history (case 6) of one of the patients treated with L-phenylalanine mustard is as follows:

Case 6. R. L., male, aged 56 years.

1952: Failing vision of the left eye. Malignant melanoma diagnosed by attending oculist. Enucleation refused.

1955: Enucleation of the left eye performed. May, 1957: Recurrence in left orbit noted.

June 26, 1957: Admitted to the hospital because of progressive weight loss, weakness and "bone" pain. Examination revealed metastases to the lungs, liver and skeleton.

June 28 to October 4, 1957: Treated with L-phenylalanine mustard, the daily oral dose varying from 12.0 to 4.0 mg. The total dose administered over the three-month period, 716.0 mg. Significant hematologic findings are shown in table 3.

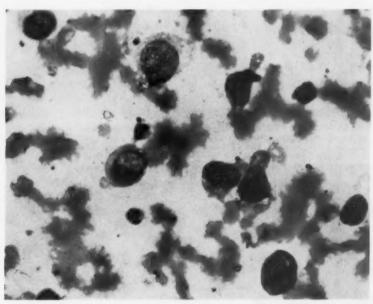


Fig. 14. Case 6. Photomicrograph of a bone marrow smear made on June 26, 1957, prior to the institution of treatment with L-phenylalanine mustard. Melanoma cells, many containing pigment, were abundant; erythropoiesis and myelopoiesis were suppressed. × 625.

Case Summary: The oral administration of L-phenylalanine mustard in a patient with metastatic melanoma of the bone marrow resulted in an apparent significant reduction in the number of melanoma cells in the marrow, temporary improvement in erythropoiesis and myelopoiesis, and improvement in the anemia. However, the suppressive action of the compound on hemopoiesis became evident by the development of leukopenia, neutropenia and thrombocytopenia three months after the institution of therapy, necessitating first a reduction in dosage, and then total withdrawal of the drug. Shortly thereafter, large numbers of melanoma cells again were found in the bone marrow.

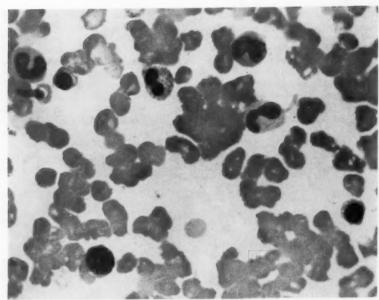


Fig. 15. Case 6. Photomicrograph of bone marrow smear, made on August 28, 1957, two months after instituting treatment with L-phenylalanine mustard. Erythropoiesis and myelopoiesis were improved, and melanoma cells were extremely rare. × 625.

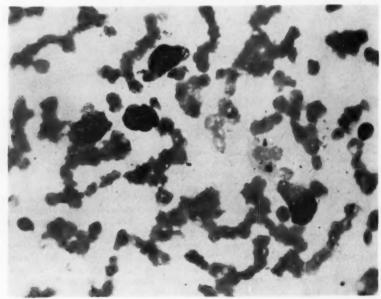


Fig. 16. Case 6. Photomicrograph of bone marrow smear, made on October 10, 1957. Two weeks after cessation of L-phenylalanine therapy, melanoma cells had reappeared in great numbers. \times 500.

TABLE 3

| Date | Hgb., gm. | RBC | WBC | Polys, | Platelets | Bone Marrow Findings |
|----------|--------------|------------|-------|--------|-----------|--|
| 6/26/57 | 9.8 | 3,140,000 | 8,000 | 92 | 358,000 | Melanoma cells present; erythropoiesis and myelopoiesis reduced (figure 14 |
| 8/28/57 | 11.7 | 3,930,000 | 4,300 | 76 | 147,000 | Melanoma cells very rare; erythropoi- esis and myelopoiesis improved (fig- ure 15) |
| 9/25/57 | 9.8 | 3,080,000 | 3,650 | 31 | 76,000 | _ |
| 10/10/58 | 12.1* | 3,900,000* | 5,800 | 67 | 260,000 | Reappearance of melanoma cells; de- creased erythropoietic and myelo- poietic activity (figure 16) |

* Following blood transfusions.

SUMMARY AND CONCLUSIONS

An attempt has been made in this paper to show that certain chemotherapeutic agents, known to produce significant degrees of remission in the malignant hemopoietic diseases (leukemia, malignant lymphoma, etc.), also may cause significant and at times prolonged degrees of regression of metastatic or recurrent lesions of the "solid" tumor type. While chemotherapeutic agents are most useful when administered on a systemic basis in the presence of widely disseminated cancer, there are certain situations in which their use locally has proved to be beneficial (e.g., transitional cell carcinoma of the urinary bladder). It is becoming increasingly evident that, with every new chemical agent worthy of clinical trial, widespread testing against a wide spectrum of human malignant diseases is indicated, not only at different dosage levels but also by different modalities of administration.

ADDENDUM

Cases 3, 4 and 5 are living and clinically free of malignant disease in February, 1960.

ACKNOWLEDGMENTS

The authors wish to express their gratitude to the following physicians who permitted them to use their cases in this report: Dr. R. S. Pollack, Dr. E. W. Denicke, Dr. C. Mc-Lennon, Dr. L. R. Reynolds, Dr. T. S. Schulte and Dr. O. Rappaport. Leukeran was supplied by Burroughs Wellcome & Company, Tuckahoe, N. Y., and thio-TEPA by Lederle Laboratories Division, American Cyanamid Company, Pearl River,

N. Y., for the studies reported in this paper.

SUMMARIO IN INTERLINGUA

Un crescente interesse in le chimotherapia de cancere durante le passate annos ha resultate in un acceleration del parada de compositos chimic que es novemente presentate al evalutation clinic de lor proprietates anti-crescential in le morbos neoplastic human. Certes de iste compositos possede un restringite spectro de activitate anti-tumoric, afficiente solmente un o duo morbos maligne, durante que altere agentes se distingue per un multo plus extense spectro de activitate. Assi, omne nove agente debe esser testate contra un extense serie de neoplasmas. Il es necessari non solmente determinar le optime nivellos de dosage sed etiam essayar varie modalitates de administration. Per consequente, le meticulose evalutation de un sol composito non

pote esser complite intra pauc menses sed require usualmente precise studios durante periodos de inter un e duo annos o plus.

Il es ben cognoscite que le majoritate del agentes de alkylisation que es currentemente in uso clinic produce varie grados de remission in certe morbos maligne afficiente le systema hematopoietic (particularmente le leucemias chronic e le lymphomas maligne), sed certes inter illos possede etiam un activitate anti-crescential contra certe tumores "solide". Variationes in le spectro de activitate de certes de iste agentes es indicate in le sequente lista.

1. Le specificiate de busulfano (Myleran) contra chronic leucemia granulocytic

(e certe casos de acute leucemia granulocytic).

 Le alique plus extense spectro de activitate del oral mustarda de nitrogeno, Leukeran, contra leucemia lymphocytic, lymphoma giganto-follicular, lymphosarcoma, morbo de Hodgkin, e casos sporadic de carcinoma non-differentiate.

3. Le ancora plus extense spectro de activitate del ethylenimina, melamina triethylenic, contra metastatic carcinoma ovarian e chronic leucemia granulocytic como

etiam contra chronic leucemia lymphocytic e le lymphomas maligne.

4. Le activitate anti-tumoric de un altere ethylenimina, Thio-Tepa (thiophosphoramida triethylenic) in inoperabile o metastatic carcinoma a cellulas transitional del vesica urinari, in carcinoma ovarian, e in carcinoma mammari (repression de effusion pleural) como etiam in chronic leucemia lymphocytic e in le morbos lymphomatose.

Le methodos del administration del agentes alkylisante es satis variabile. Le vias oral, intravenose, e intramuscular es utilisate pro obtener un effecto systemic in extensemente disseminate morbos neoplastic, sed in casos special le injection intracavitari o intratumoric del agente chimotherapeutic se ha provate utile. In certe casos, maligne effusiones (pleural, pericardial, o peritonee) de occurrentia secundari a lymphoma maligne, carcinoma ovarian, carcinoma mammari, etc. pote esser reprimite durante septimanas o menses per le injection intracavitari de melamina triethylenic, Thio-Tepa, o mechlorethamina. Thio-Tepa ha etiam essite usate con un certe grado de successo in injectiones local in inoperabile carcinomas del vesica urinari e del prostata quando altere mesuras therapeutic habeva remanite sin effecto palliative. Tamen, le methodo del injection local de Thio-Tepa in inoperabile tumores es deciditemente restringite in su utilitate.

Il es importante signalar emphaticamente que le tractamento con agentes de alkylisation in morbos maligne de humanos es, in le caso le plus favorabile, de efficacia palliative. Tamen, il es equalmente importante signalar e sublinear que iste agentes produce a vices remissiones que permitte al patiente ducer un existentia multo plus confortabile que lo que esseva possibile ante le discoperta de iste compositos.

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A CLINICAL STUDY OF THYROID STORM * †

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INTRODUCTION

Thyroid storm or crisis is a severe, often fatal exacerbation of the manifestations of hyperthyroidism, which requires prompt recognition and energetic treatment if the patient is to survive. The use of iodide and thiourea compounds to prepare the hyperthyroid patient for surgery has virtually eliminated post-thyroidectomy storm. That thyroid storm occurs in other than the immediate post-thyroidectomy period, however, has been well recognized since early in this century. Unhappily, storm and its attendant mortality continue to be observed during the course of untreated or partially treated thyrotoxicosis. Today, most deaths attributable to hyperthyroidism are due to such "spontaneous" or "medical" storm. Clearly a need exists for prevention, early recognition and adequate treatment of medical thyroid storm.

The purpose of the present report is to review our experience with the clinical manifestations of 21 episodes ‡ of thyroid storm observed at the Cook County Hospital from 1955 to 1958, and to report the effectiveness of reserpine and steroids in reducing mortality.

DEFINITION OF THYROID STORM

The criteria for the diagnosis of storm are not absolute. The diagnosis depends primarily upon clinical judgment. McArthur and associates ³ defined thyroid storm as a "life-endangering augmentation of the symptoms of thyrotoxicosis." There is general agreement that in addition to the exaggerated manifestations of hyperthyroidism, fever, marked tachycardia and signs of central nervous system, cardiovascular, hepatic and gastrointestinal dysfunction are prominent.¹⁻⁸ In this study, thyroid storm was considered to be present whenever accentuated signs and symptoms of hyperthyroidism were accompanied by a fever of 100° F. or greater, and marked tachycardia.

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CLINICAL FEATURES

Incidence: Twenty-one episodes of thyroid storm were observed in 20 patients. One patient (case 1) had two distinct episodes of storm, an unusual event which has been reported before. Twenty episodes were medical storms as defined above; 14 of these patients survived. One episode was post-thyroidectomy storm, and here too the patient survived. During the same years, 284 cases of hyperthyroidism were admitted to the hospital. Thus, the incidence of thyroid storm in patients hospitalized for hyperthyroidism was 7%. Others have reported the incidence to vary from 2% to 8%. 3, 7, 8

Sex, Race and Age: In table 1, the distribution of patients according to sex, race and age is compared to a series of 159 hyperthyroid patients without storm observed by the authors during the same period. The sex and age distribution in patients with storm did not differ significantly from

TABLE 1
Distribution of Patients (1955-1958)

| indicion of Latients (1700 1700 | 1 |
|---------------------------------|---|
| Thyroid Storm (20 Patients) | Hyperthyroidism without Storm (159 Patients) % 15 |
| 80 | 85 |
| 30 70 | 17 83 |
| | |
| 0 15 35 | 4 22 23 |
| 30 | 19 |
| 10 | 14 |
| 10 | 12 |
| 0 | 6 |
| | Thyroid Storm (20 Patients) |

the usual distribution in thyrotoxicosis. The large proportion of Negroes in both groups reflects the composition of the hospital population. More patients with storm were white than is usually found to be the case in hyperthyroidism in this hospital. The significance of this observation is unknown. The age distribution in this series is comparable to that reported by McArthur et al.³ All ages were represented except children, who were not studied, and the very old. There was no indication in this study that storm is more common over the age of 40 years, as has been suggested. 10, 11

Season: The onset of storm was independent of the season of the year, in contrast to Crile's 12 finding that storm is more likely to occur in the summer.

Previous Thyroid Disease: Prior to the appearance of storm, all patients exhibited the manifestations of thyrotoxicosis. The duration of prestorm hyperthyroidism was from two to six months in 12 episodes, from seven to

12 months in six episodes, and from one to four years in the remainder. All six fatalities occurred in patients with antecedent hyperthyroidism of less than six months' duration. Three patients had had goiters for 18 months to 18 years before becoming hyperthyroid. The severity of the prestorm hyperthyroidism was estimated from the histories. It was severe in nine patients, moderately severe in 11, and mild in only one. The average weight loss before storm was 30 pounds; this varied from as little as five pounds in six months to as much as 80 pounds in 10 months.

Onset: In 15 episodes, thyroid storm was ushered in abruptly by an acute exacerbation of the signs and symptoms of hyperthyroidism. Four of these occurred in hospitalized patients under observation. In the remainder, the transition from thyrotoxicosis to storm was gradual.

Precipitating Factors: Storm often follows shortly upon a complicating illness or traumatic event during the course of hyperthyroidism. Such precipitating factors were noted in 12 episodes in the present series (table 2).

TABLE 2
Precipitating Factors

| rrecipitating ractors |
|---|
| Single factor8 |
| Pelvic inflammatory disease Appendicitis with rupture Bronchopneumonia Subacute bacterial endocarditis Tooth extraction Palpation of thyroid gland Insulin reaction Fear |
| Multiple factors |
| Upper respiratory infection, propylthiouracil withdrawal and subtotal thyroidectomy Propylthiouracil withdrawal, radioactive iodine therapy and pulmonary embolism Preëclampsia and cesarean section Preëclampsia and forceps delivery |
| None9 |

A single precipitating factor was identified in eight, and multiple factors in four episodes. In this series, infections and surgical procedures were the factors most frequently found. Most of the infections were acute; one, subacute bacterial endocarditis, was chronic (case 2). Storm followed two major surgical procedures, thyroidectomy and cesarean section, and two minor procedures, forceps delivery and a dental extraction. The obstetric procedures were performed for preëclampsia. That the trauma need not be surgical is illustrated by case 3, who developed storm soon after a large group of medical students palpated his goiter. Sudden stress induced by pulmonary embolism (case 4) and by insulin reactions appeared to provoke storm in two instances. In one episode, storm followed closely upon a severe fear reaction when the patient was threatened with a gun (case 5). In two

episodes, storm was preceded by withdrawal of propylthiouracil in the belief that the patient was ready for definitive therapy. In one, an upper respiratory infection developed between drug withdrawal and thyroidectomy. In retrospect, the infection produced an exacerbation of thyrotoxicosis, and thyroidectomy then precipitated storm. In the other, definitive therapy was radioactive iodine. Two weeks later, a pulmonary embolism precipitated storm (case 4). Storm has been reported to follow radioactive iodine therapy, 13 but in this instance the pulmonary embolism appears to have been a more likely precipitating factor. All of the above precipitating factors have been previously reported. 1-8, 14-18 Other precipitating factors found in previous studies include diabetes mellitus with keto-acidosis 17, 18 and digitalis intoxication.11 In this series, one patient was diabetic and one developed digitalis intoxication during the course of treatment. In neither instance, however, did these factors appear to precipitate the thyroid storm.

TABLE 3 Physical Findings in 21 Episodes of Thyroid Storm

| Temperature (°F.) | 15 Survivors | 6 Fatalities |
|---|------------------|------------------|
| 100-102.9 | 7 | 2 |
| 103-106.8 | 8 | 4 |
| Heart rate (min.) | | |
| 100-139 | 4 | 1 |
| 140-169 170-200 | 10 | 3 2 |
| Pulse pressure (mm. Hg) | | |
| 40-59 | 5 | 3 3 |
| 60-100 | 10 | 3 |
| Thyroid gland | | |
| Type / Nodular | 4 | 1 |
| Diffuse | 11 | 1 5 1 5 |
| Size Not enlarged Moderately large (2×) | 0 8 | 1 |
| Size Moderately large (2×) Very large (3-4×) | 7 | 0 |
| Exophthalmos | 11 | 1 |
| Pretibial myxedema | 2 | 0 |
| Central nervous system | | |
| Psychosis | 5 | 1 |
| Coma | 2 | 2 |
| Apathy Confusion | 5 2 2 5 | 1 2 1 1 |
| Cardiovascular system | | |
| Congestive failure | 7 | 3 |
| Arrhythmia | 4 | 1 |
| Gastrointestinal system | | |
| Jaundice | 2 | 3 2 |
| Diarrhea | 6 | 2 |

It should be emphasized that in nine episodes of storm, no precipitating factor could be identified.

Physical Findings (table 3): The signs of thyroid storm differ from those of hyperthyroidism only by a tendency to be multiple and more intense.³ The appearance of the patient was most striking. Mental and emotional disturbances were observed in 19 episodes. Six patients were frankly psychotic; indeed, two had been admitted initially to the psychopathic wards, one in a catatonic schizophrenic state and the other actively hallucinating. The others were wildly agitated and out of contact with reality. In contrast, four patients were comatose, and three were somnolent and apathetic. Six patients presented mental confusion and were disoriented. Unusual restlessness and emotional lability, even for hyperthyroidism, were noted in nine patients. Striking asthenia of both axial and peripheral musculature was present in eight patients. Ten patients appeared to be emaciated and cachectic. A soft, smooth, moist, flushed skin was common in the whites. In the Negroes, a silky, hyperpigmented skin with a glistening sheen was frequent.

Fever greater than 100° F. is a cardinal manifestation of thyroid storm, for in our experience and that of others 1 it does not occur in uncomplicated thyrotoxicosis. In 12 instances, the temperature ranged from 103 to 106.8° F. Such hyperpyrexia was found in both those who died and those who lived. Fever could be attributed to a coexisting infection in only four episodes of storm.

A marked tachycardia is characteristic of the patient in storm. In 16 episodes, a ventricular rate of 140 per minute or greater was observed, and in three the rate exceeded 170 per minute. Atrial flutter was found once, and atrial fibrillation four times. The blood pressure did not differ greatly from that usually seen in hyperthyroidism. A pulse pressure of 60 to 100 mm. Hg was found during 13 episodes of storm. Diastolic hypertension was present in three patients. In one it could be attributed to preëclampsia, and in a second, to essential hypertension, but in the third patient it was present only during storm, and returned to normal with recovery.

Goiter and exophthalmos, the classic signs of hyperthyroidism, were also present in the patients with storm. In 15 patients the thyroid gland was markedly enlarged, that is, three or more times greater than normal size. In one patient the gland was not enlarged. Both multinodular and diffuse goiters were found. Exophthalmos was observed in 12 patients, and the usual eye signs of hyperthyroidism were elicited in most. Other characteristic features of hyperthyroidism, such as tremor, the Plummer nail sign, lymphadenopathy and splenomegaly were noted. Interestingly, two previously untreated patients had pretibial myxedema when first observed.

Cardiovascular, hepatic and gastrointestinal disturbances are frequent in storm.¹⁻⁸ Congestive heart failure was present in 10 episodes. In only three episodes was an underlying etiology other than thyrotoxicosis recog-

nized: essential hypertension, rheumatic heart disease with subacute bacterial endocarditis, and preëclampsia. The last occurred in the patient who had two episodes of storm (case 1). In her second episode, when there was no pregnancy, congestive failure did not recur. The edema due to heart failure was usually mild, although one patient presented with anasarca. Cardiomegaly and nonspecific apical systolic murmurs were frequent, even in patients not in failure. Jaundice was observed in five patients, four of whom had congestive heart failure as well. There were no physical findings indicative of primary hepatic disease. Gastrointestinal manifestations consisted primarily of diarrhea and, only occasionally, of vomiting.

As seen in table 3, there were no clinical findings characteristic of the

patient who was to die in storm.

Laboratory Findings (table 4): Extended laboratory studies during storm were not feasible because of the urgent need for treatment. Studies performed before or after storm reflected only the usual findings of partially treated hyperthyroidism. This was particularly true of the thyroid function tests. It was not possible to secure basal metabolic rates or radioactive

TABLE 4
Laboratory Findings in Thyroid Storm

| Tests | No. Pts. Studied | No. Abnormal | Observed Range of Abnormal Results |
|-------------------------------------|---------------------|--------------|---------------------------------------|
| Thyroid function | | | |
| Cholesterol (mg. %) | 18 | 16 | 55-147 |
| Protein bound iodine (µg.%) | 2 | 2 | 13.5, 20+ |
| BMR (%)* | 10 | 10 | +24 to +61 |
| Radioactive iodine uptake (24 hr.)* | 11 | 11 | 51-93 |
| Hepatic function | | | |
| Icterus index (U) | 12 | 5 | 19-77 |
| Cephalin flocculation | 13 | 6 | 3+ to 4+ |
| Thymol turbidity (U) | 13 | 7 | 5.7-16 8 |
| Alkaline phosphatase (B.U.) | 12 | 6 | 5.1-10.6 |
| Total protein (gm. %) | 20 | 2 | 5.1, 5.7 |
| Albumin (gm.%) | 9 | 2 7 | 2.0-3.6 |
| Globulin (gm. %) | 9 | 4 | 3.8-5.4 |
| Gamma globulin (gm.%) | 13 | 9 | 1.3-3.0 |
| Electrolytes | | | |
| Sodium (mEq./L.) | 14 | 6 | 123-135† |
| Chlorides (mEq./L.) | 14 | 2 | 83, 95† |
| Potassium (mEq./L.) | 14 | 3 | 2.8-3.0† |
| Calcium (mg.%) | 11 | 1 | 8.2 |
| Phosphorus (mg. %) | 13 | i | 5.3 |
| Blood urea nitrogen (mg.%) | 19 | 2 | 43, 104 |
| Blood sugar (mg.%) | 13 | 4 | 139-250 |
| Hemogram | | 1 | 107 200 |
| Hemoglobin (gm.%) | 21 | 15 | 7.0-11.5 |
| Red blood cells (million/mm.²) | 15 | 8 | 2.4-3.7 |
| White blood cells (mm.²) | 20 | 10 | 2.1 0.7 |
| Increased | 20 | 8 | 11.000-56.200 |
| Decreased | | 2 | 3,900, 4,200 |

^{*} Tests performed following recovery from storm.

[†] In addition, case 6 with adrenal insufficiency had a serum sodium level of 107, chloride 80, and potassium 7.0 mEq./L.

iodine uptake studies during storm and, unfortunately, facilities for determining protein-bound iodine were not available throughout most of the period of study. The average basal metabolic rate in the survivors was plus 35%, emphasizing that considerable hyperthyroidism remains after recovery from storm. Twenty-four hour radioactive iodine uptakes in the survivors averaged 69%. Protein-bound iodine during storm was obtained in only two patients, and was 13.5 μ g.% in a patient who survived, and above 20 μ g.% in a patient who died (case 5). Scattered reports have shown the protein-bound iodine to vary from 11 to 15 μ g.% ^{16, 18, 19} in spontaneous storm, and as high as 19.5 μ g.% in a case due to acute thyroid poisoning.²⁰ The serum cholesterol level determined during storm averaged 118 mg.%, and was below normal in all but two instances.

Hepatic function tests are often abnormal in hyperthyroidism.⁶ The icterus index varied from 19 to 77 units in five patients. Abnormal elevations of the cephalin-cholesterol flocculation, the thymol turbidity and the alkaline phosphatase tests were not uncommon. An elevation of the serum gamma globulin level greater than 1.70 gm. % was noted in seven patients. In the patients with storm, then, icterus was the outstanding hepatic abnormality. Hepatic tests, although indicating hepatocellular damage, were not characteristic of a specific lesion. The patients were too ill for liver biopsy.

The serum electrolyte levels and water balance were fairly well maintained in most of the patients in spite of diarrhea, vomiting and sweating. Moderate depression of the level of serum sodium was observed in one-half of the episodes. Marked electrolyte changes were observed only in a patient who died with adrenal insufficiency (case 6). Abnormal serum calcium and phosphorus levels were observed but once. The latter is of interest in view of a recent report in which potentiation of experimental thyroid storm in animals by infusions of phosphate solutions was demonstrated.²¹

An increased incidence of hyperthyroidism in diabetics has been reported,²² and several instances of diabetic acidosis and concurrent thyroid storm have been described.^{17, 18} It is therefore not surprising that transient glycosuria, acetonuria and hyperglycemia were found in a few patients, only one of whom was a known diabetic.

Renal function did not appear to be grossly affected by storm. Moderate proteinuria was observed in 11 episodes, and could not be distinguished from that ordinarily found during febrile episodes or in congestive heart failure. The urinary sediment was uniformly unremarkable. Azotemia was noted preterminally in two patients.

The blood picture in hyperthyroidism is usually within normal limits, ¹¹ but in our experience, mild anemia is not uncommon. Yet a hemoglobin level of less than 12.0 gm.% was observed frequently in thyroid storm. There was no evident explanation for the anemia. Bone marrow aspirations were not performed. Leukopenia was noted twice, once in the patient with pneumonia. Leukocytosis, on the other hand, was noted eight times, and

in only one of these was an underlying infection present. Interestingly, in two patients with infection the white blood count was normal. Thus, seven instances of leukocytosis without infection and attributable to storm alone were found. The highest count in these was 56,200 per cubic millimeter. Relative and absolute lymphocytosis, stated to be common in thyrotoxicosis, was found five times, with absolute counts varying from 4,000 to 6,900 per cubic millimeter.

Course and Complications (table 5): The duration of storm in the survivors varied from one to eight days, with an average of three days. Typically, the survivors responded to intensive therapy rapidly, with control of restlessness, slowing of the heart rate, and beginning defervescence within 12 hours. Steady improvement was usual thereafter, and by the end of 72 hours, two thirds were afebrile, alert, oriented, hungry, and out of danger. The remaining survivors responded less dramatically, but were well controlled within a week. An eight-day course was observed in a patient whose condition was not appreciated initially. Upon administration of steroids

TABLE 5 Course of Thyroid Storm

| | 15 Survivors | 6 Fatalities |
|-------------------------|--------------|--------------|
| Average duration (days) | 3 | 7 |
| Longest duration | 8 | 25 |
| Shortest duration | 1 | 1 |
| Complications | | |
| Number of patients | 2 | 2 |
| Suppurative parotitis | 0 | 2 |
| Adrenal insufficiency | 0 | 1 |
| Digitalis intoxication | 0 | 1 |
| Pseudomonas meningitis | 1 | 0 |
| Pelvic abscess | 1 | 0 |

six days after onset of storm, however, response was rapid and the patient was controlled within two days. Cases 1 and 3 typify a favorable response to therapy.

Following recovery from storm, all patients were overtly thyrotoxic, both clinically and by measurement of basal metabolic rates. There was nothing noted to distinguish poststorm thyrotoxicosis from the usual case of hyperthyroidism. The poststorm period was uneventful in all but two patients: one, whose storm was precipitated by a ruptured appendix, went on to develop a pelvic abscess which eventually resolved on antibiotic therapy; the other developed meningitis on the seventh poststorm day, and was cured after a protracted course. It is noteworthy that despite the infections, continuous use of antithyroid medication apparently prevented recurrence of thyroid storm in these two patients. All but one survivor (case 1) remained in the hospital until definitive therapy was given. The duration of treatment between the episode of storm and definitive therapy varied from three to 14 weeks, and averaged six and one-half weeks.

In the fatalities, storm lasted from one to 25 days, with an average duration of seven days. The longest course was observed in a 58 year old Negro woman whose storm was not recognized at first. By the time therapy for storm was begun, congestive heart failure, digitalis intoxication and jaundice were significant complications. Even so, initial response to treatment was favorable, but when suppurative parotitis developed she succumbed. Rheumatic pancarditis, adrenal insufficiency and toxic hepatitis were factors contributing to death in cases 2, 6 and 7, respectively. Another fatality occurred in the patient with diabetes mellitus who developed congestive heart failure and jaundice during storm. Despite therapy she died in five days. On the other hand, no complication was evident to explain the failure to respond to intensive therapy in one patient treated for nine days (case 5).

TREATMENT

Prophylaxis: Prevention of storm should be the major objective of treatment. The virtual elimination of post-thyroidectomy storm by proper preparation of the hyperthyroid patient for surgery has been a significant accomplishment in this direction. To so eliminate spontaneous medical storm, early diagnosis, prompt treatment, and measures to avoid storm are necessary in every hyperthyroid patient. It is important to realize that fever, with or without coexistent infection, is an indication for treatment for storm, even if the actual existence of storm is in doubt. Fever in thyrotoxicosis should never be considered to be due to infection alone; when infection is overt, treatment for both storm and infection is indicated. Specific measures to avoid storm include the prohibition of palpation of the thyroid in the severely thyrotoxic patient, and the postponement of any surgical procedure or other manipulation whenever possible in every hyperthyroid patient until he is euthyroid. If surgery is necessary, specific treatment for storm (see below) should be instituted and maintained until the patient is out of danger. Reactions to drugs, such as digitalis and insulin, should be prevented by careful management. Antithyroid drugs should not be withdrawn for diagnostic or other purposes until the hyperthyroidism is well controlled.16

Active Treatment: As experience with thyroid storm was gained, the following plan of therapy was evolved. All elements of it have been reported previously (table 7), but we believe this to be the first series in which reserpine and hydrocortisone have received extensive trial.

Symptomatic Therapy: Measures directed toward maintenance of hydration and nourishment, control of hyperpyrexia, and relief of anoxia are of great value. Two to three liters daily of intravenous glucose and water or normal saline or both are usually sufficient to maintain water and electrolyte balance. Moderate fever can be treated with aspirin, but when hyperpyrexia occurs, alcohol sponges, wet towels, ice packs or ice mattresses are

indicated in addition. Anoxia is combatted by administration of oxygen. Other symptomatic therapy is given depending upon the circumstances.

Specific Therapy: Control of the manifestations of thyroid storm is essential if the patient is to survive. This is accomplished by measures which decrease the formation and release of thyroid hormone and counteract its peripheral action. To block further synthesis and release of thyroid hormone, 23-25 iodine is given as sodium iodide intravenously in doses of 1 to 3 gm. daily, or as Lugol's solution orally, in doses of 30 to 60 drops daily, and propylthiouracil is given orally (or by intubation in comatose patients) in doses of 600 to 1,000 mg. daily. To control the peripheral manifestations of storm, reserpine 19 is given intramuscularly in doses of 2.5 mg. every four to eight hours. Hydrocortisone, in doses of 100 to 300 mg. daily, is given intravenously or intramuscularly, not only to control peripheral manifestations and to counteract the stress of storm, but also to offset the possibility of relative or absolute adrenal insufficiency.²⁸⁻²⁸ Because of this possibility, hydrocortisone seems preferable to ACTH. Finally, specific complications, such as infection or congestive heart failure, are treated by appropriate measures. As the patient improves, drugs are given orally instead of parenterally, doses are decreased to maintenance levels, and hydrocortisone is gradually withdrawn.

Results of Therapy and Prognosis: The effects of specific therapy were striking in this series. Defervescence and improvement in the general condition of the patient were often noted within hours after the institution of ACTH or hydrocortisone therapy. The mechanism by which this improvement was brought about is unknown. Restlessness and tachycardia, in particular, responded to reserpine, often in 12 to 24 hours. Since its use was not attended by respiratory depression, reserpine appears to be much superior to morphine, which has been used customarily for control of restlessness. The requirement for sedatives and hypnotics was reduced or obviated when reservine was used. Side-effects from the drug, such as hypotension, were not observed. It is our impression that recovery from storm was primarily effected by the use of hydrocortisone, ACTH and reserpine. Iodine and propylthiouracil appeared to have little effect upon the manifestations of storm and, we believe, served mainly to prevent release of additional thyroid hormone. Other agents, such as promazine and related drugs, were used in some patients and had visible sedative effect. They did not appear to be so useful as reserpine in this regard. Because sympathetic blockade may prevent manifestations of experimental thyrotoxicosis,20 phentolamine was used in one patient but was without visible effect (case 5). A similar failure has been reported previously. 18

In this series, six of the 21 episodes of storm terminated fatally, an over-all mortality rate of 28.6%. Case 7 died before treatment was instituted. Therefore, the mortality rate in the 20 treated episodes was 25%. As seen in table 6, therapy in both survivors and fatalities was comparable.

TABLE 6

| The | erapy | |
|--|--------------|--------------|
| During storm | 15 Survivors | 6 Fatalities |
| Number of cases treated | 15 | 5 |
| Iodides | 15 | 5 |
| Propylthiouracil Steroids without reserpine | 11 | 5 |
| Reserpine without steroids | 1 | 0 |
| Steroids and reserpine | 9 | 3 |
| Following storm | | |
| Subtotal thyroidectomy | 3 | |
| Radioactive iodine | 10 | |
| No treatment | 2* | |

* Includes one patient with post-thyroidectomy storm and one patient with two episodes of storm who finally received radioactive iodine (case 1).

The factors responsible for survival or death are not readily discernible. Hyperpyrexia, extreme tachycardia, mental disorders, congestive heart failure and jaundice occurred with approximately equal frequency in both groups, and it is noteworthy that patients with *or without* these severe manifestations died from, or survived, thyroid storm (table 3).

It is difficult to obtain an accurate estimate of expected mortality in thyroid storm. That prognosis was generally held to be extremely poor in past years is indicated by the failure of many early reports to discuss survival at all (table 7). Reports of single cases of storm, in which survival or death occurred, are not infrequent, 13-18, 30 but conclusions as to mortality rates cannot be drawn from them. In table 7 an attempt is made to compare therapy and mortality from reports which deal with more than one case. Using iodine as specific therapy, Bansi 7 reported 78% mortality. McArthur and co-workers 3 reported 67% mortality in 36 cases. If their last

Table 7
Representative Results of Therapy for Thyroid Storm, 1928–1959

| | | | Specific | Therapy | | No. of | N- of | |
|-------------------------|------|---------|-------------------|---------------------|-----------|--------|------------------|--------|
| Author (Reference) | Year | Iodides | Thiourea Drugs | Steroids or ACTH | Reserpine | Cases | No. of Deaths | % Died |
| Lahey 1 | 1928 | + | | | | 6 | 6 | 100* |
| Bayley 2 | 1934 | + | | | | 51 | 51 | 100° |
| Ransom and Bayley 4 | 1934 | + | | | | 37 | 37 | 100* |
| Pemberton 5 | 1936 | + | | | | 4 | 2 | 50 |
| Maddock et al. 6 | 1937 | + | | | | 88 | 88 | 100* |
| Bansi 7 | 1939 | + | | | | 32 | 25 | 78 |
| Waldenström 10 | 1945 | + | | | | 10 | 3 | 30 |
| McArthur et al. 8 | 1947 | + | | | | 36 | 24 | 67 |
| Rives and Shepard 8 | 1951 | + | + | | | 25 | 10 | 40 |
| Szilagyi et al. i | 1952 | + | + | + | | 4 | 0 | 0 |
| Canary et al. 19 | 1957 | | | | + | 2 | 0 | 0 |
| Rawson and Sonenberg 31 | 1959 | + | + | + | | 7 | 2 | 28 |
| This series | 1959 | + | + | + | + | 21 | 6 | 28 |

* Only mortality reported.

four cases, who received adrenal cortical extract and propylthiouracil in addition, are excluded, then the mortality in their series with the use of iodine alone approximated 75%. Rives and Shepard,8 reporting an over-all mortality of 40% with iodine therapy, noted that 100% of their spontaneous storm cases died. By contrast, Waldenström 10 reported survival of all of his patients who received iodides. It seems conservative to estimate that when iodine was the only specific therapy, the mortality rate in thyroid storm approximated 60 to 70%. With the reports of use of adrenal cortical extract or ACTH, a more favorable experience is apparent. McArthur and co-workers, and later, Rawson and Sonenberg,31 reported survival of patients treated with adrenal cortical extract. Szilagvi 9 reported survival in storm when ACTH was used. In the present series (table 6), the patient survived in 14 of the 18 episodes in which ACTH or hydrocortisone or both were used, a mortality rate of 22%. This is considerably better than the use of iodine alone or in combination with propylthiouracil. Although we could discern no difference in the use of ACTH or hydrocortisone, for reasons previously discussed we now recommend and use hydrocortisone in preference to ACTH. Reserpine, by itself, has been shown to abort storm. 19 In this series it was used but once without steroids in addition (table 6). We do not recommend its use as sole therapy, but concur that it is a most valuable addition to therapy.

Definitive Therapy after Storm: Following recovery from storm, three patients were treated by subtotal thyroidectomy, the remainder by radioactive iodine (table 6). Significantly, all three patients undergoing thyroidectomy had postoperative tachycardia and fever, and were treated by intravenous fluids, iodides and reserpine. Although these episodes were rapidly controlled, they have led us to conclude that poststorm patients retain the propensity for this complication until hyperthyroidism has been controlled for a considerable period. We therefore do not now elect to treat definitely by thyroidectomy. Should the procedure be indicated for other reasons, we recommend the use of iodides and steroids before and during surgery, and reserpine in addition afterwards to prevent recrudescence of storm. Radioiodine therapy, on the other hand, was tolerated very well. We consider it the therapy of choice, unless contraindicated on other grounds. Even so, it is advisable that the patient be thoroughly controlled before radioiodotherapy. Premature withdrawal of antithyroid medication may permit a relapse of thyroid storm.16 Such a premature attempt at therapy may have played a part in the fatal outcome of case 2. The course after successful definitive therapy was no different from that seen in the usual hyperthyroid patient treated by these measures.

PATHOLOGY

Autopsies were performed in four of the six fatal cases. The thyroid glands varied from 30 to 110 gm. in weight. Three presented the features

of untreated hyperthyroidism. Grossly they were firm and meaty in appearance, and microscopically they showed depletion to absence of colloid, heaped-up columnar epithelium with papillary projections, engorged capillaries, and lymphocyte infiltration of interstitial tissue. On the other hand, one thyroid showed considerable involution. The patients had been treated for from one to 17 days.

The pituitary glands were normal in each case. An enlarged thymus was found once. Except for the one patient with bilateral adrenal hemorrhage (case 6), adrenal findings were confined to depletion of lipid content.

Lymphorrhage was noted in only one case.

The paucity of specific anatomic changes other than those in the thyroid gland in patients dying in thyroid storm has been noted previously by Foss et al.³²

COMMENT

The pathogenesis of thyroid storm is unknown. Although various explanations have been offered, 11 definite conclusions cannot be drawn from the available evidence.

Is thyroid storm merely unusually intense hyperthyroidism due to marked secretion of thyroxin? Storm has been reported to follow acutely upon ingestion of large amounts of thyroxin,^{20, 38} and upon the administration of triiodothyronine to an already hyperthyroid patient.³⁴ On the other hand, it appears that the amount of circulating thyroxin in storm, estimated by the concentration of protein-bound iodine, is often not uniquely high.³⁵ Furthermore, very high levels of protein-bound iodine have been found after thyroidectomy or radioiodotherapy without concomitant storm.^{36, 37} The fact that administration of large amounts of desiccated thyroid ³⁸ or triiodothyronine ³⁹ to the hyperthyroid patient ordinarily does not induce storm also indicates that something besides the quantity of circulating thyroxin is responsible.

Thyroid storm has been called "decompensated thyrotoxicosis," ³ implying an exhaustion of the tolerance of the body to the excess hormone. There are indeed features in storm which lead one to conclude that an abnormal metabolic response to the hyperthyroidism is at the root of the problem. The absence of characteristic pathologic findings, as shown in this and other studies, ³² suggests a primary disturbance of chemistry rather than of structure. ⁶ Epinephrine is in some way linked to the peripheral manifestations of thyroid hormone, ²⁹ and phosphate intensifies experimental thyrotoxicosis. ²¹ Yet characteristic abnormalities of the concentration of these substances in the blood have not been found in thyroid storm. ⁶ The findings suggesting deficient adrenal reserve in thyrotoxicosis ^{27, 28} perhaps provide one clue to the disordered metabolism in storm. Steroids are used therapeutically for the purpose of counteracting the "stress" of storm. May their demonstrated usefulness in fact be due to supplementation of failing adrenal

glands? The hyperthyroid individual develops storm when increased metabolic demands are introduced from extrathyroidal sources, such as infection and trauma. These sources similarly are often responsible for precipitating crisis in Addison's disease.

Regardless of the role of extrathyroidal factors in the precipitation of thyroid storm, it is inescapable that protracted hypersecretion of thyroid hormone is fundamental to thyrotoxicosis and to the development of storm. A well controlled hyperthyroid patient does not develop thyroid storm. Our experience with this complication emphasizes the need for control of hyperthyroidism without delay, and the importance of avoiding the burden of increased metabolic demands, whenever possible, until euthyroidism is reestablished.

SUMMARY

Twenty-one episodes of thyroid storm were observed in 20 hyperthyroid patients from 1955 to 1958. Fourteen of 20 "medical storms" were nonfatal, as was one post-thyroidectomy storm. The incidence of storm in all patients hospitalized for hyperthyroidism was 7%. The distribution of patients according to sex and age was comparable to that of hyperthyroidism without storm.

Prestorm thyrotoxicosis was in general severe, and of less than one year's duration. Six patients were under treatment but still hyperthyroid when storm developed. In three fourths of the episodes, onset of storm was abrupt.

Precipitating factors included infection, surgery remote from the thyroid gland, thyroidectomy, excessive palpation of the thyroid, pulmonary embolism, fear, and reaction to insulin. Important among contributing factors was propylthiouracil withdrawal. No precipitating factor was apparent in nine episodes.

Storm was recognized as a severe exaggeration of all manifestations of hyperthyroidism associated with fever greater than 100° F. (in 12 episodes, greater than 103° F.), and marked tachycardia (in 16 episodes, greater than 140/minute). Mental disturbances, congestive heart failure, jaundice and diarrhea were common. Both multinodular and diffuse goiters of varying size were found.

Symptomatic therapy included maintenance of hydration, control of hyperpyrexia, and relief of anoxia. Specific therapy included intravenous or oral iodide, propylthiouracil, intramuscular reserpine and parenteral ACTH or hydrocortisone. Because of the possibility of adrenal insufficiency, hydrocortisone seems preferable to ACTH. The survivors usually responded to therapy promptly and recovered in an average of three days. In the fatalities, storm lasted an average of seven days.

This study emphasizes the need for early recognition and prompt control of hyperthyroidism to prevent storm. Prior to the attainment of euthyroid-

ism, antithyroid treatment should not be interrupted and the patient should be protected against infection, trauma, unnecessary procedures, surgery or other situations which add to the metabolic burden. When these are unavoidable, treatment for storm should be instituted as a prophylactic measure. The mortality rate of storm has been reduced from approximately 60 to 70% to near 25% by the use of reserpine and steroid hormones, in addition to iodine and antithyroid drugs. It is anticipated that the use of these agents whenever thyroid storm is imminent will further reduce the mortality from this serious complication of uncontrolled thyrotoxicosis.

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SUMMARIO IN INTERLINGUA

Vinti-un episodios de "tempesta thyroide" esseva observate in 20 patientes hyperthyroide inter 1955 e 1958 al Hospital del Contato Cook. "Tempesta thyroide" esseva definite como un exacerbation-a grados impericulante le vita del patiente-in le manifestationes de thyrotoxicosis, associate con febre de plus que 100 F e con tachycardia marcate. Vinti del episodios esseva spontanee o medical, i.e., in illos le tempesta occurreva in le curso de hyperthyroidismo a tractamento incomplete o non tractate del toto. Un episodio sequeva thyroidectomia subtotal. Le incidentia de tempesta in patientes hospitalisate pro hyperthyroidismo amontava a 7 pro cento. Le distribution per sexo e per etate esseva simile a illo trovate in hyperthyroidismo sin tempesta. Le curso del hyperthyroidismo ante le tempesta esseva generalmente sever e de un duration de minus que un anno. Le declaration del tempesta esseva abrupte in 15 episodios. Le plus frequentemente observate factores precipitatori esseva infection e extrathyroide interventiones chirurgic. Altere factores incontrate esseva palpation excessive del glandula thyroide, formas sever de timor, embolismo pulmonar, e reaction a insulina. In novem del episodios, nulle factores precipitatori poteva esser identificate.

Omne le patientes se trovava apparentemente in statos de thyrotoxicosis sever. Omnes—con un exception—habeva strumas de dimensiones palpabile e de typo multinodular o diffuse. Un medietate del patientes habeva exophthalmia. Disturbationes
mental e emotional—i.e. coma, psychosis, confusion, etc.—esseva observate in 19
episodios. Congestive disfallimento cardiac esseva presente in 10 episodios. Un
subjacente etiologia altere que hyperthyroidismo poteva esser trovate in solmente tres
de istes. Cinque patientes exhibiva jalnessa. Febre de plus que 103 F occurreva
in 12 episodios. Isto poteva esser attribuite a infection in solmente quatro episodios.
Le frequentia del pulso excedeva 140 per minuta in 16 episodios. Le studios laboratorial produceva resultatos pauco remarcabile. Tests del function thyroide esseva
postponite necessarimente usque post le fin del tempesta, e alora illos corroborava
simplemente le existentia de hyperthyroidismo.

Le therapia symptomatic visava a mantener le stato de hydratation, a bridar le hyperpyrexia, e a alleviar le anoxia. Le therapia visante specificamente a blocar le formation e liberation de hormon thyroide e a meliorar su manifestationes peripheric consisteva in administrationes de ioduro de natrium per via intravenose, de propylthiouracil per via oral, de reserpina per via intramuscular, e de hydrocortisona per via intravenose. Omne iste drogas esseva usate in grande doses. Frequentemente

le resultatos del therapia esseva frappante, con rapide defervescentia e relentation del pulso, claration del stato mental, e restablimento in inter 24 e 72 horas. Sex patientes moriva. Le plus importante constatation necroptic esseva hyperthyroidismo. Inadvertentemente un del patientes non recipeva le tractamento. Le mortalitate in comparation con le mortalitate de inter 60 e 70 pro cento que esseva reportate in le passato quando iodo o drogas antithyroide esseva le sol agentes specific in uso.

Le cosa vermente desirate es le prevention del tempesta thyroide. Prompte diagnose e tractamento de hyperthyroidismo va esser de adjuta in le attingimento de iste objectivo. Usque le momento ubi un stato de euthyroidismo es effectuate, le therapia antithyroide non debe esser interrumpite e le patiente debe esser protegite contra infection, trauma, manipulationes non vermente necessari, incluse interventiones chirurgic, e altere factores que augmenta le carga metabolic. Quando influentias de iste generes non pote esser evitate, therapia pro tempesta thyroide debe esser instituite como mesura prophylactic. Il pare justificate predicer que le uso de reserpina e hormones steroide—a parte iodo e drogas antithyroide—quandocunque un episodio de tempesta thyroide pare imminente va reducer additionalmente le mortalitate causate per iste serie complication de thyrotoxicosis non bridate.

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BACTEREMIA DUE TO COAGULASE-POSITIVE STAPHYLOCOCCUS AUREUS*

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The purpose of this investigation was to help to define the problem of staphylococcic infections by a detailed clinical study of 100 cases of staphylococcic bacteremia. Since most observers agree that there are no significant differences between strains of staphylococci causing fatal infections and those isolated from healthy carriers, it may be assumed that patients infected with staphylococci differ from the majority of people, in regard either to their environment or to their innate resistance.^{1, 2, 3, 4}

The fact that 50 of the 100 cases of bacteremia that we are reporting developed infections in the hospital indicts this environment. However, 48 of our patients developed infections outside the hospital, and this suggests that innate factors of resistance also may be involved.

The place of onset, portal of entry, age, race, sex, cause of hospital admission, significant history, methods of diagnosis, physical findings, laboratory determinations and results of therapy in the 100 patients studied are being presented, along with a comparison of our findings and those of other investigators. It is hoped that this information will point out factors in the hospital environment and in the patients themselves the understanding of which may help to prevent and to treat serious staphylococcic infections.

MATERIALS AND METHODS

One hundred cases of bacteremia due to coagulase-positive Staphylococcus aureus that occurred at the Milwaukee County General Hospital between the years 1951 and 1958 were studied. The majority of the cases were seen by one of us at the bedside (B. A. W.), and the charts of all patients were studied jointly by the co-authors. Initial selection of the cases was from the records of sensitivity studies done in the Infectious Disease Control Unit laboratory, and a case was used for study if a perusal of the chart satisfied both investigators that the positive blood culture was of clinical significance and had, in fact, played a part in the patient's disease. Thus, a few cases were rejected either because the culture may have been a contaminant or because an invasion of the blood stream appeared to have

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Table 1
Place of Onset of Staphylococcic Bacteremia and Its Possible
Influence on Mortality

| | Total Number | Mortality |
|---|-----------------|-----------|
| Cases that probably developed out of the hospital | 50 | 56% |
| Cases that developed while patient was in the hospital for another reason | 48 | 73% |
| Undetermined place of onset | 2 | |

been agonal. Cases that came to our attention because of postmortem examination were not included. Therefore, all cases were diagnosed during life, even though in a few instances clinical recognition of this fact apparently was not made. Examination of the charts was done in as objective a fashion as possible, in that results of therapy were always decided upon before the results of sensitivity tests were looked at, and the opinion as to where the infection started always was arrived at before the outcome of the case was observed. In instances where the two investigators could not agree on a point, it was put down as indeterminate. Details of the method used to study separate factors will be included in separate results. Throughout the

Table 2
Phage* Types of Staphylococci Isolated from Five Patients Who Developed Their Infections at Home, and from Seven Patients Who Developed Infections in the Hospital

| Case No. Infec- tions Established at Home | Portal of Entry | Phage Type | Case No. Infec- tions Caught in Hospital | Portal of Entry | Phage Type |
|---|-----------------|------------|--|-------------------------|------------|
| 29 | Undetermined | 53/77 | 6 | Respiratory tract | 53 |
| 40 | Undetermined | 5.3 | 17 | G.U. tract | Nontypable |
| 4.3 | G.I. tract | 75/44A | 22 | Thoracentesis | 99/42B |
| 54 | Skin | Nontypable | 26 | Transurethral resection | 47 |
| 80 | Skin | 3A/55/44A | 48 | Appendec- tomy | 53/VA4 |
| | | | 7.3 | Cutdown | 4A4/44A |
| | | | 88 | ? | 53/VA4 |

Breakdown of Phage Types

| Type | No. of Cases | Type | No. of Cases |
|------|--------------|------|--------------|
| 53 | 2 | 53 | 3 |
| 44A | 2 | VA4 | 3 |
| 77 | 1 | 44A | 1 |
| 75 | 1 | 47 | 1 |
| 55 | 1 | 99 | 1 |
| 3A | 1 | 42B | 1 |

^{*} Phage types were kindly determined by Dr. M. Koch in the laboratory at the Veterans Hospital, Wood, Wisconsin.

entire study the fatal and nonfatal cases were considered separately, as well as together, to determine possible factors which might have influenced prognosis.

RESULTS

Place of Onset: Fifty cases probably developed outside the hospital, and 48 cases probably developed after the patient had entered the hospital (table 1). The mortality was not significantly higher in the patients who developed bacteremia in the hospital. Bacteriophage * typing was done on

TABLE 3
Portal of Entry in Staphylococcic Bacteremia

| Portal | Case Numbers | Total Number | Mortality 82% | |
|---|---|----------------------------------|------------------|--|
| 1. Operative Procedure Cystoscopy Transurethral resection Hip pinning Abdominal surgery Paracentesis Cutdown for infusions Teeth extraction | 10,* 25,* 23 12,* 26,* 9* 19, 87,* 97,* 59,* 79* 20,* 24, 53,* 60,* 69, 70* 22* 90,* 65,* 73* 30* | 22 3 3 5 6 1 3 | | |
| 2. Respiratory Tract | 1,* 4,* 6,* 7,* 13,* 16, 51,* 78,* 96,* 29,* 42, 44,* 63,* 35, 38, 92,* 74,* 77, 78,* 83, 85* | 21 | 71% | |
| 3. Skin | 3, 14, 25,* 28, 52,* 54,* 56, 99, 50* 11,* 41,* 91, 93, 94,* 95,* 72,* 75, 76,* 80,* 82, 8 | 21 | 55% | |
| 4. Genitourinary Tract | 17,* 25,* 26,* 53,* 86, 89,* 29,* 50,* 33,* 27, 97,* 58,* 34, 39, 95,* 71,* 81 | 17 | 71% | |
| 5. Gastrointestinal Tract | 2,* 100, 43,* 60,* 64, 47 | 6 | 50% | |
| 6. Sinuses | 45, 46 | 2 | 0 | |
| 7. Biliary Tract | 5 | 1 | 0 | |
| 8. Middle Ear | 57* | 1 | 100% | |

^{*} Fatal cases are indicated by asterisks in all the tables.

seven strains isolated from patients with hospital infections, and on five strains isolated from patients who entered the hospital with bacteremia. The so-called epidemic hospital strains were found in cases of bacteremia which developed outside the hospital environment, and some of the cases that had developed in the hospital were from strains of nondescript reputation (table 2).

Portal of Entry: The most common portal of entry of the staphylococcus in this series of cases was an operative procedure (table 3). Five cases

^{*}Phage typing was kindly done by Dr. M. Koch, of the Veterans Hospital, Wood, Wisconsin.

Negro Female

Total, 3

developed after the pinning of a hip and six after abdominal surgery. Almost equally important as portals of entry were the respiratory tract, skin and genitourinary tract (table 3). Sporadic cases developed from the biliary tract, sinuses, gastrointestinal tract and the middle ear. The highest mor-

TABLE 4
Age, Sex, Race and Mortality of 100 Cases of Bacteremia
Due to Staphylococcus aureus

| Race, Sex of Patients | Age Ranges in Years | | | | | | | | | | | |
|---------------------------|----------------------------|------------------------|---|---------------------|---|--------------------|---------------------------------|-------------------|--------------------------|----------|-------------------------|--------------------------------|
| | 1-10 | | 11-20 | | 21-30 | | 31-40 | | | 41-50 | | |
| | Fatal | Nonfatal | Fatal | Nonfatal | Fatal | Non | fatal | Fatal | Nonfatal | Fa | tal ! | Nonfatal |
| White Male Total, 57 | | #82 | | #46, #47 | | | | #4, #7, #80 | | # 5 | 50, # | 5, #16, 18, #21, 83, #93 |
| White Female Total, 31 | | | | | #30 #90 | #45 | | #31 #36 | | | 19, 15, 17, 18 | #75 |
| Negro Male Total, 9 | | #56, #35, #99, #100 | | - A | # 52 | #8, | #14 | | #32 | | | |
| Negro Female Total, 3 | | | # 58 | | | | | | | | | #34 |
| | | | | | Age Ran | ges in | Years | | | | | |
| Race, Sex of Patients | 51-60 | | 61-70 | | 71-80 | | 81-90 | | | Mean Age | | |
| | Fatal | Nonfatal | Fatai | Nonfatal | Fata | 1 : | Vonfat | al Fa | ital Nor | ıfatal | Fatal | Nonfata |
| White Male Total, 57 | #6, #72, #74, #92 | # 23, | #12, 15, 25, 29, 43, 44, 48, 55, 60, 68, 41, 78 | #27, #64, #77 | #2, # #17, 3 #51, # #79, # #88, # | \$9. 53. 87. | #81. #91 | * | 13, 26, 54, 63, | | | 49 |
| White Female Total, 31 | #62 | #24. #28 | #57, #61, #70, #97 | | #20, # #73, # #85, # #40 | 76, | # 42, # 69, # 86, # 38 | # # # 1 | | | | 58 |
| Negro Male Total, 9 | | | #84 | | | | | | | | 48 | 15 |

tality was in the postoperative bacteremias. The next most lethal portals of entry were the respiratory tract and the genitourinary tract (table 3).

#33

Age, Race, Sex: The patients ranged from one to 93 years in age (table 4). The predominant group of patients consisted of white males between the ages of 61 and 90 (38 patients). Only 10% of the patients were Negroes. This is below the percentage of Negroes in our hospital, and

TABLE 5
Cause of Admission to the Hospital

| Cause of | Admission to the | e Hospital |
|--|--|---|
| Cause | Number of Cases | Case Number |
| Fever | 31 | 34, 37, 38, 39, 40, * 16, 24, 31, * 27, 42, 44, * 45, 35, 36, * 24, 25, * 46, 47, 48, * 49, * 89, * 51, * 55, * 57, * 64, 71, * 72, * 77, 80, * 83, 85* |
| Pain in chest | 7 | 14 68 * 42 78 * 1 * 2 * 10* |
| Burns | 6 | 14, 68,* 42, 78,* 1,* 2,* 10* 99, 11,* 52,* 56, 75, 82 |
| Coma | 5 | 40 * 44 * 57 * 81 7* |
| Chills | 4 | 40, * 44, * 57, * 81, 7* 16, 24, 49, * 55* 18, 79, * 6, * 87* |
| Fractured hip | 4 | 18. 79.* 6.* 87* |
| Rectal bleeding | 4 | 20,* 69, 76*, 94* |
| Shortness of breath | 4 | 20,* 69, 76*, 94* 67,* 74,* 85,* 92* |
| Weakness | 4 | 32, 16, 53,* 73* 5, 61,* 73* |
| Vomiting | 3 | 5, 61,* 73* |
| Pneumonia | 3 | 28, 44,* 35 |
| Pain in hip | 3 | 37, 39, 15* |
| Abdominal pain | 2 | 61,* 68* 31,* 34 |
| Convulsion | 2 | 31,* 34 |
| Cough Diabetes | 2 | 16, 38 7,* 72* |
| Elective surgery | 2 | 70,* 12* |
| Furunculosis | 2 | 91, 3 |
| Headache | 2 | 45, 46 |
| Heart failure | 2 | 18, 22* |
| Iaundice | 2 | 5, 64 |
| Leg ulcers | 2 | 41,* 84* |
| Pain in legs | 2 | 93, 50* |
| Peptic ulcer | 3 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 | 3, 60* |
| Abscess, right hip | 1 | 59* |
| Acidosis | 1 | 72* |
| Acute abdomen | 1 | 48* |
| Anemia | 1 | 43* |
| Anorexia | 1 | 53* |
| Arthritis Auto accident | 1 | 15* 66 |
| Benign prostatic hypertrophy | î | 26* |
| Bleeding ulcer | i | 63* |
| Bowel obstruction | i | 17* |
| Cirrhosis | 1 | 65* |
| Confusion | 1 | 13* |
| Diarrhea | 1 | 16 |
| Endocarditis | 1 | 30* |
| Fainting spell | 1 | 3 |
| Hematuria | 1 | 9* |
| Herpes zoster | 1 | 54* |
| Mental observation | 1 | 29* 33* |
| Myocardial infarct Pain in left thigh | 1 | 62* |
| Paronychia | | 23 |
| Periorbital edema | | 30* |
| Pelvic inflammatory disease | | 58* |
| Psychosis | | 88* |
| Pyelonephritis | 1 | 27 |
| Renal shutdown | 1 | 90* |
| Rundown condition | | 86 |
| Senility | | 13* |
| Shock | | 43* |
| Stupor | | 95* |
| Urinary retention | | 10* |
| Weight loss | 1 | 68* |

TABLE 6

Significant Associated Diagnoses in 100 Cases of Bacteremia Due to Coagulase-Positive Staphylococci

| Diagnosis | Number of Cases | Case Numbers |
|---|------------------|---|
| Pneumonia | 20 | 6,* 7,* 16, 1,* 2,* 35, 38 96,* 14, 28, 26,* 68,* 42, 51,* 73,* 77, 81, 83, 85,* 93 |
| Diabetes | 12 | 96 * 14, 28, 26, 68, 42, 51, * 73, * 77, 81, 83, 85, * 93 24, 7, * 23, 50, * 72, * 49, * 83, 93, 95, * 64, 68, * 79* |
| Pyelonephritis | 10 | 95,* 10,* 39, 32, 27, 43,* 45, 59,* 71,* 86 |
| Bacterial endocarditis | 8 | 21, 18, 22,* 67,* 12,* 15,* 30,* 36* |
| Cirrhosis of the liver | 7 | 87,* 65,* 73,* 22,* 37, 53,* 42 11,* 52,* 56, 75, 82, 99 |
| Burns | 6 | 11,* 52,* 56, 75, 82, 99 |
| Wound infection | 4 | 24. 6.* 19. 79* |
| Rheumatic heart disease | 4 | 18, 22,* 76,* 68* |
| Multiple abscesses, furuncles or ulcer | 3 | 50,* 91, 41* 41,* 40,* 68* 55,* 74,* 92* |
| Arteriosclerosis | 3 3 | 41,* 40,* 08* |
| Cancer of the lung | 3 | 33, 14, 92 |
| Tuberculosis | 2 | 32, 4,*70* 61,*53* 9,*10* |
| Cancer of the pancreas Cancer of the prostate | 2 | 01, 55 |
| Diarrhea | 2 | 89,* 100 |
| Hepatitis | 2 2 2 2 | 32, 64 |
| Meningitis | 2 | 55,* 57* |
| Osteomyelitis of hip | 2 | 37, 62* |
| Pelvic inflammatory disease | 2 | 58,* 34 60,* 78* |
| Ruptured peptic ulcer | 2 | |
| Senile psychosis | 2 | 13, 88* |
| Sinusitis | 2 | 46, 45 |
| Dermatitis | 1 | 3 |
| Appendicitis | 1 | 48* 26* |
| Prostatic hypertrophy | 1 | 9* |
| Bleeding duodenal ulcer Brucellosis | 1 | 32 |
| Cerebral vascular accident | 1 | 84* |
| Cancer of the breast | î | 20* |
| Cancer of the rectum | î | 20* |
| Cellulitis | 1 | 54* |
| Chronic bronchitis | 1 | 40* |
| Common duct stone with obstruction | 1 | 15* |
| Diverticulitis | 1 | 73* |
| Gastroenteritis | 1 | 98* |
| Glomerulonephritis | 1 | 4* 54* |
| Herpes zoster | 1 | 33* |
| Hypertension Incarcerated hernia | 1 | 17* |
| Infectious mononucleosis | - 1 | 47 |
| Lupus erythematosus | î | 31* |
| Malnutrition | i | 53* |
| Multiple myeloma | 1 | 76* |
| Multiple sclerosis | 1 | 23 |
| Osteomyelitis of spine | 1 | 66 |
| Otitis media | 1 | 57* |
| Pernicious anemia | 1 | 43* |
| Pericarditis | 1 | 80* |
| Pleurisy | 1 | 78* |
| Polycythemia | 1 | 78* 17* |
| Postoperative septicemia | 1 | 17* |
| Pulmonary embolism | 1 | 90* |
| Renal shutdown | I | 90 |

suggests an increased resistance to staphylococci in this race. There was not a significant sex differentiation. As might be expected, the mortality was greater in the older ages.

Cause of Admission to the Hospital: In no case was the diagnosis of staphylococcic bacteremia suggested on admission. The most frequent reasons for hospital admission were fever (31 cases), burns (six cases), coma (five cases), fractured hip (four cases), and abdominal pain (four cases) (table 5).

Associated Diagnoses: The diseases with which staphylococcic bacteremia was associated most commonly were pneumonia (20 cases), diabetes (12 cases), pyelonephritis (10 cases), cancer (nine cases), bacterial endocarditis

Table 7
Previous Infections Suffered by 48 of the Patients with Bacteremia Due to Coagulase-Positive Staphylococcus aureus

| Infection | Number of Patients | Case Number |
|-----------------------------|--------------------|--------------------|
| Pelvic inflammatory disease | 1 | 34 |
| Tuberculosis | 3 | 25, 33, 70 |
| Cellulitis | 8 | 71, 72, 98, 35, |
| | | 44, 68, 43, 19 |
| Cystitis | 1 | 39 |
| Cholecystitis | 1 | 89 |
| Chronic bronchitis | 3 | 9, 4, 44 |
| Chronic dermatitis | 3 | 80, 19, 44 |
| Colitis | 1 | 24 |
| Decubiti | 2 | 43, 94 |
| Fistula in ano | 1 | 34 |
| Gangrene | 1 | 94 |
| Hepatitis | 1 | 64 |
| Leg ulcer | 2 | 41, 98 |
| Osteomyelitis | 1 | 95 |
| Lupus erythematosus | 1 | 31 |
| Rheumatic fever | 5 | 18, 21, 36, 67, 68 |
| Bacterial endocarditis | 1 | 22 |
| Sinusitis | 1 | 45 |
| Syphilis | 2 | 97, 87 |
| Thrombophlebitis | 1 | 61 |

(eight cases), and cirrhosis (seven cases). Perusal of the associated diseases shows that in some instances the term "associated" may be misleading, since, for instance, the endocarditis and pneumonias were often caused by the staphylococci, whereas the diabetes, cancer and some cases of pyelone-phritis would be more truly called "associated."

Past History of Infections: The history of previous illnesses recorded either by the resident, the intern or the student was examined to determine some incidence of previous infections in the patients (table 7). Eight patients had had cellulitis in the past, but, taken as a whole, these data would seem to indicate that the patients had not previously been prone to bacterial infections.

Diagnosis: The diagnosis in each case was established by one or more blood cultures that grew coagulase-positive Staphylococcus aureus at a time

TABLE 8

Reason for Cultures Being Taken in 100 Cases of Staphylococcic Bacteremia

| Reason | Number of Case |
|--|----------------|
| Fever {Fatal, 54 Nonfatal, 31} | 85 |
| Murmurs and subacute bacterial endocarditis, suspected | 7 |
| Pneumonia | 6 |
| Chills | 3 |
| Wound sepsis | 2 |
| Anemia | 1 |
| Presence of abscess on back | 1 |
| Suspected bacteremia | 1 |
| Urinary tract infection Wound infection | 1 |
| wound injection | 1 |

when there was objective evidence on the chart which supported the opinion that the patient was suffering from a bacteremia. The most important tool for diagnosis was of course the blood culture, and in 85 of the cases the blood culture was drawn because the patient was running a fever (table 8).

An analysis of the blood cultures drawn during the course of the bacteremias revealed that 63% of 155 cultures drawn before therapy were positive, while only 40% of 212 cultures drawn during therapy were positive. This is consistent with our previous study of bacteremia in bacterial endocarditis, which showed that if a bacteremia is present, the majority of blood cultures drawn are positive. Therefore, the overenthusiastic drawing of multiple blood cultures after five have been negative is rarely justifiable.

TABLE 9

Physical Findings in 100 Cases of Bacteremia Due to Staphylococcus aureus

| | Mean in Survivors | | | Mean in Fatal Cases | | | Mean in Total Group | | |
|-----------------------------------|-------------------|--------|------------------|---------------------|-----------|-------|---------------------|-----------|-----------|
| | Before | During | After | Before | During | After | Before | During | After |
| Pulse—(beats per minute) | 88 | 101 | 87 | 86 | 102 | | 88 | 102 | 87 |
| Respiration (breaths per minute) | 22 | 27 | 21 | 21 | 26 | | 22 | 26 | 21 |
| Temperature corrected to oral °F. | 100.1 | 101.8 | 98.2 | 99.8 | 101.1 | | 100 | 101.4 | 98.2 |
| Blood pressure | $\frac{126}{75}$ | 124 | $\frac{131}{68}$ | $\frac{130}{72}$ | 126 73 | | 128 73 | 126 73 | 131 68 |

Number of Patients in Whom Finding Was Observed

| | Survivors | Fatalities | Totals |
|---------------------------|-----------|------------|--------|
| Palpable spleen | 3 | 8 | 11 |
| Palpable liver | 5 | 20 | 25 |
| Skin lesions | 12 | 33 | 45 |
| Abnormal sensorium | 11 | 63 | 74 |
| Abnormal cardiac findings | 17 | 30 | 57 |

The lower percentage of positive cultures that were drawn while the patient was receiving therapy would be expected, but this finding should emphasize that it is often worth while to draw a blood culture even though the patient is receiving an antibiotic.

In only 44 cases was the initial chief complaint of the patient related to the bacteremia. This illustrates the value of blood cultures in all cases where the cause of a fever is not apparent, since the clinical signs other than fever do not often point to the diagnosis of bacteremia. The rule of our medical service that a blood culture must be drawn before antibiotics are administered to a patient undoubtedly resulted in the diagnosis of some of these patients.

Table 10

Cardiac Findings in 100 Cases of Bacteremia Due to Coagulase
Positive Staphylococcus

| E E | | , | , | | |
|--------------------------|--|--|---|-------|--------------------------------------|
| Physical Finding | Number of Fatal Cases in Whom Lesion Was Ob- served | Total | Number of Nonfatal Cases in Whom Lesion Was Observed | Total | Total Number of Times Observed |
| Mitral systolic murmur | 29, 67,* 50, 40, 49, 57, 55, 12, 36,* 11, 22, 98 | 12 14, 16, 37, 64, 82, 42, 86, 38, 34, 21,* 37 | 32, 42, 86, 38, | | |
| Aortic systolic murmur | 29, 30,* 67, 68, 22*, 26 | 6 | 18* | 1 | 7 |
| Mitral diastolic murmur | 67 | 1 | 18* | 1 | 2 |
| Aortic diastolic murmur | iastolic murmur 33, 80 | | 21 | 1 | 3 |
| Enlargement of the heart | 36, 29, 33, 10, 54, 55, 67, 41, 78, 80, 54, 4 | 12 | 38, 21 | 2 | 14 |
| Arrhythmia | 36, 41, 30, 31, 50, 15 | 6 | 27 | 1 | 7 |
| Pericardial friction rub | 33 | 1 | | | 1 |
| | | 40 | | 17 | 57 |

^{*} Cases of endocarditis.

Physical Findings: Significant physical findings are summarized in tables 9, 10 and 11. The pulse, temperature and respirations increased during the illness, with no significant differences between the survivors and the fatalities. The mean blood pressures remained essentially stable in both the fatal and the nonfatal groups. However, there was a paucity of recordings of blood pressure during the terminal stages of some patients. The shocklike picture of gram-negative bacteremia was rarely seen.⁶

Possible common denominators among the physical findings were skin lesions (45 patients), an abnormal sensorium (74 patients), cardiac disease (57 patients), hepatomegaly (25 patients) and splenomegaly (11 patients). All of these findings were more common in the fatal cases.

A wide variety of skin lesions was described (table 9). The most common was petechiae, which were found in eight cases. All of these cases were fatal, but only two were due to bacterial endocarditis. If we accept petechiae as being due essentially to endothelial damage, this might be a clue to the pathogenesis of fatal staphylococcic bacteremia, i.e., generalized endothelial damage. The fact that 45 cases had skin lesions, some of which antedated their bacteremia, lends credence to a concept of the skin as an important portal of entry. 18-10

Table 11

Breakdown of Skin Lesions Observed in 100 Cases of Staphylococcic
Bacteremia Due to Coagulase-Positive Staphylococci

| Lesion | Numbers of Fatal Cases in Whom Lesion Was Observed | Total | Numbers of Surviving Cases in Whom Lesion Was Observed | Total | Total Numbe of Times Observed |
|--|---|-------|---|--------|-------------------------------------|
| Abscesses | 50, 73, 76 | 3 | 75, 28, 91 | 3 | 6 |
| Burns | 11, 52 | 2 | 99, 56, 82 | 3 | 5 |
| Cellulitis | 44, 54, 71, 72 | 4 | | - | 4 |
| Butterfly rash | 67 | 1 | | | 1 |
| Decubitus lesions | 41, 43 | 2 | 28 | 1 | 3 . |
| Dermatitis | 62, 80 | 2 | | -07000 | 2 |
| Herpes simplex | 63 | 1 | - | | 1 |
| laundice | 65, 53 | 2 | 64 | 1 | 3 |
| Leg ulcers | 41, 84 | 2 2 | _ | | 2 |
| Macular rash on face and arms | 31 | 1 | | | 1 |
| Drug eruption | 62 | 1 | | | 1 |
| Petechiae | 22, 31, 48, 55, 67, 68, 12, 30 | 8 | - 1 | - | 8 |
| Purpuric spots over the ankles | 36, 30 | 2 | _ | ** | 2 |
| Splinter hemorrhages in toenails | 68 | 1 | - | _ | 1 |
| Ulcerated wound infections | 73, 79 | 2 | | _ | 2 |
| Ecchymosis | _ | - | 28 | 1 | 1 |
| Erythematous papules over lower abdomen | - | | 39 | 1 | 1 |
| Paronychia | | - | 23 | 1 | 1 |
| Eczema of scrotum | _ | | 14 | 1 | 1 |

The cardiac findings were not particularly striking when the eight cases of endocarditis were excluded (table 9), and probably would be found in a comparable group of patients of the same age without bacteremia. Myocarditis was diagnosed antemortem only once (case 7), but study of sections of the heart muscle of the patients who died may reveal a higher incidence of this complication.

Laboratory Findings: The mean hemoglobin level dropped approximately 1 gm. during the course of the bacteremia, but the fatal cases were not significantly more anemic than those that survived (table 10). The mean white blood counts rose to 17,600 during the disease. Patients who died did not have a significantly higher white blood count. The percentages of polymorphonuclear cells rose from 72.7 to 80, but survivors and fatalities again were not different in this respect. "Stab" counts were not compared because of the variation in interpretation of stab cells among technicians.

Nonprotein nitrogen levels rose from a mean of 41 to 50.8 mg.% in the fatal cases, but dropped from 46 mg.% to 31.5 mg.% in the survivors. This was the sole laboratory finding in which a significant difference was found between the survivors and the fatalities.

The mean sedimentation rate was 81 mm. per hour in the 40 patients in whom this determination was made. The rate was not significantly higher in the fatalities.

Serum proteins were determined in 37 patients. The mean serum albumin was 2.8 gm.%, and the mean globulin, 3.5 gm.%. The lower albumin figure is of some interest, particularly in view of the few cirrhotics included in this series of patients.

There were abnormal findings on urinalysis of one kind or another in the majority of the patients. Thirty-one had significant albuminuria, three had significant glycosuria (the diabetics were apparently well controlled), 12 had hematuria and 24 had pyuria. As might be expected by the findings in regard to nonprotein nitrogen concentration, the patients who died had more abnormal findings in their urine. However, it should be noted that the patients who died increased their urine output in spite of the mean rise in nonprotein nitrogen. This is of particular interest because this was also found in bacteremia due to gram-negative bacilli.⁶

Comments on Therapy: Our remarks regarding therapy must be prefaced by the comment that it was manifestly unsatisfactory, because 64% of our patients died. We did not attempt to rationalize how many of the patients died from associated illness and how many died solely from the bacteremia, but felt that a majority of the fatalities might not have occurred if the staphylococcus had not entered the picture. We will restrict our remarks to therapy with the antibiotics and not belabor the obvious fact that all underlying factors must be treated to the maximum. Maintenance of fluid balance, urinary output, cardiac output, an adequate airway, and a satisfactory level of hemoglobin are of equal value to the antibiotics, and in many cases surgical drainage is more important than any other single therapeutic effort. However, during this study an attempt was made to evaluate therapy with the antibiotics, and these findings appear to be worthy of presentation. The correlation between in vitro sensitivity tests and clinical results has already been published.¹¹ The significant findings were as follows:

- 1. When the organism isolated from the blood was sensitive to 6 μ g./ml. or less of any of the antibiotics tested, there was a 55% chance of response to that antibiotic.
- When the staphylococcus isolated from the blood was resistant to 6 μg./ml. or greater of any of the antibiotics tested, less than 1% chance of response was likely.¹¹

Thus sensitivity tests by the tube dilution method 12 were of definite value in telling which drugs would not be effective, but in vitro sensitivity to an

Table 12

Laboratory Findings in 100 Cases of Bacteremia Due to Coagulase-Positive

Staphylococcus aureus

| Determination | Mean in Fatal Cases or Number of Cases with Positive Findings | | | Mean in Survivors or Number of Cases with Positive Findings | | | Combined Mean or Number of Cases with Positive Findings | | | Significant Difference |
|--|---|----------------|-------|---|--------------|-------|---|----------------|-------|---------------------------|
| | Before | During | After | Before | During | After | Before | During | After | |
| Hemoglobin concentrations in gm. % | 11.6 | 10,8 | | 12.4 | 11.4 | 13,1 | 12.0 | 11.1 | 13.1 | _ |
| White blood count in thou- sands per cu. mm. | 11,0 | 19,8 | | 7.4 | 15.4 | 8.8 | 9.2 | 17.6 | 8.8 | - |
| Per cent of polymorphonu- clear leukocytes | 74.8 | 83.7 | | 70.1 | 78.0 | 67.0 | 72.7 | 80.8 | 67.0 | |
| Nonprotein nitrogen in mg.% | 41 | 50,8 | | 46.1 | 31.5 | 34 | 43 | 41 | 31.5 | + |
| Sedimentation rate in milli- liters per hr., Westergren method | | 70.7 (25) | | | 81.7 (15) | | | 81.2 | | - |
| Albumin concentration in blood in gm. % | 3.4 (4) | 2.72 (26) | | 4.4 | 2.9 (11) | | | 2.8 (37) | | - |
| Globulin concentration in blood in gm. % | 3.3 (4)* | 3.7 (26)* | | | 3.4 (11)* | | | 3.5 (37)* | | _ |
| 2+ or greater albuminuria | | 24 | | 7 | | | 31 | | | - |
| Glycosuria | | 2 | | | 1 | | 3 | | | |
| Significant hematuria | | 8 | | 4 | | | 12 | | | |
| Significant pyuria | | 20 | | 4 | | | 24 | | | |
| Urine output in milliliters per day | 1,267 (5)* | 1,437 (24)* | | | 980 (6)* | | | 1,209 (30)* | | |

^{*()} Numbers in parentheses show the number of determinations used to get the means.

antibiotic would in no way guarantee a clinical response. Table 13 illustrates the value of determining the sensitivity of causative strains of staphylococci to the antibiotics. When they were used without regard to sensitivity tests a mean response of 26% was obtained, whereas when antibiotics were used against sensitive strains a 55% response was obtained.

TABLE 13
Effectiveness of the Antibiotics When Used Against Both Sensitive and Resistant Strains and When Used Against Sensitive Strains*

| Antibiotic | % Response in A | All Cases Used | % Response Against Sensitive Strain | | | | |
|---|-----------------|------------------------|-------------------------------------|------------------------|--|--|--|
| Penicillin Chloramphenicol Erythromycin | 24 8 37 | 75/18 49/4 38/14 | 64 23 61 | 28/18 13/3 23/14 | | | |
| Tetracyclines Neomycin | 40 46 | 37/15 13/6 | 75 46 | 20/15 13/6 | | | |
| Vancomycin Novobiocin | 50 20 | 6/3 5/1 | 50 20 43 | 6/3 5/1 7/3 | | | |
| Streptomycin | Mean 26% | 19/3 | Mean 55% | 115/63 | | | |

^{*} In this analysis, indeterminate results are omitted, so the figures are not exactly the same as in our paper on the correlation of sensitivity tests with clinical results. II

This study could not be used as a means of testing the relative efficacy of the various agents because no attempt was made to randomize patients who received the various drugs, and widely different dosage schedules were used.* However, it is of some interest that penicillin, erythromycin and the tetracyclines were as effective as neomycin and vancomycin when they were used against sensitive strains. If further studies bear this out, it would suggest that the older, well established, safer antibiotics, such as penicillin, erythromycin, the tetracyclines, and possibly chloramphenicol in higher dosage than was used in this study,† should be used against strains of staphylococci sensitive to them, and that the more toxic drugs, such as vancomycin, ristocetin, kanamycin and neomycin, should be saved for strains of staphylococci resistant to other agents. It should be pointed out also that the "bacteriostatic" tetracyclines did just as well against sensitive strains as did "bactericidal" penicillin.

The study of the correlation between clinical results and in vitro sensitivity of the bacteria showed no instances of penicillin-resistant staphylococci (M.I.C.‡ > 6 μg./ml.) responding to penicillin, regardless of dosage. On the other hand, some cases responded to penicillin even though the staphylococci were weak penicillinase producers. 11 Thus cases 83, 91, 93, 5, 21, 24, 38 and 42 received some benefit from penicillin, even though their organisms needed from 1.5 to 6 µg./ml, of penicillin for inhibition, and were presumably penicillinase producers.11 In many of these cases there was other antibiotic therapy, so the response to penicillin may be doubted. However, as a group these cases indicated to us that weak penicillinase production does not absolutely mean that a strain will not respond to penicillin. Not one of 49 cases caused by strains of staphylococci resistant to 6 µg./ml. of penicillin showed even equivocal response to its use.11 Therefore, our findings agree with those of Wilson and Hamburger, 13 who feel that massive penicillin administration in cases of bacteremia due to penicillin-resistant organism will probably be of no avail in spite of some reports to the contrary.14 The cases (50, 57, 61, 97) of penicillin-sensitive staphylococci that did not respond to penicillin have been detailed and discussed in the separate publication.11

It is beyond the scope of this paper to discuss our present antibiotic therapy of staphylococcus bacteremia which is based upon our most recent experiences, other than to say that we use one or more of a group of agents § that include vancomycin, ristocetin, kanamycin and neomycin when the sensitivity of the strain is unknown, and treat by parenteral route as intensively as possible. If sensitivity tests show sensitivity to other agents,

^{*}Two grams per day intravenously of chloramphenicol, erythromycin, tetracyclines, neomycin, vancomycin, > 20 million units per day intravenously of penicillin, 2 gm. per day intramuscularly streptomycin, 2 gm. per day by mouth of novobiocin.
† Six grams per day intravenously of chloramphenicol succinate.

[#] Minimal inhibitory concentration, § Our preliminary studies show that vancomycin may be the safest of this group of agents, but even it has resulted in some serious toxic reactions.

TABLE 14

1958 Rank of 17 Antibiotics Against 75 Strains of Coagulase-Positive Pathogenic Staphylococci Isolated from Infections at the Milwaukee County General Hospital

| Antibiotic | Per Cent of Staphylococci Sensitive to 6 µg./ml. | Rank |
|-------------------|--|------|
| Kanamycin | 100 | 1 |
| Humatin | 100 | 1 |
| Neomycin | 100 | 1 |
| Vancomycin | 100 | 1 |
| Ristocetin | 100 | 1 |
| Novobiocin | 96 | 6 |
| Nitrofurantoin* | 84 | 7 |
| Oleandomycin | 73 | 8 |
| Erythromycin | 59 | 9 |
| Tetracycline | 56 | 10 |
| Streptomycin | 55 | 11 |
| Penicillin | 47 | 12 |
| Oxytetracycline | 40 | 1.3 |
| Polymyxin B | 40 | 13 |
| Bacitracin | 35 | 15 |
| Chlortetracycline | 35 | 15 |
| Chloramphenicol | 15 | 17 |

* Not an antibiotic, and not effective except in urinary tract infections.

we change to these and use them in maximal tolerated dosages. We use "bactericidal" agents such as penicillin, neomycin, vancomycin, kanamycin and ristocetin in cases of endocarditis. Table 14 shows our latest data on the sensitivity of staphylococci to available antibiotics as determined by a study of 75 strains of coagulase-positive staphylococci isolated at the Milwaukee County General Hospital in 1958. It is to be noted that all of the strains are sensitive to the four antibiotics mentioned.

Our final comment regarding therapy would be that, if the causative organism is sensitive to penicillin and is not a penicillinase producer (M.I.C. $<1~\mu\mathrm{g./ml.}$), this drug in massive dosage is still the antibiotic of choice (40,000,000 units per day given intravenously) because of the high dose tolerated.

We are trying to increase the effectiveness of the antibiotics by meticulous treatment of all the ancillary factors in each case, and by investigating the use of agents that appear to augment host resistance.¹⁵ It is too early to tell if these efforts will increase the survival rate.

Table 15

Mortality by Year of 100 Cases of Bacteremia Due to Coagulase-Positive

Staphylococcus aureus

| | Year | | | | | | | | |
|-----------------------|------|------|------|------|------|------|------|------|-------|
| | 1951 | 1952 | 1953 | 1954 | 1955 | 1956 | 1957 | 1958 | Total |
| Number of cases | 3 | 10 | 8 | 11 | 12 | 25 | 26 | 5 | 100 |
| Number of fatal cases | 2 | 6 | 3 | 7 | 6 | 20 | 16 | 4 | 64 |
| % Fatal | 67% | 60% | 38% | 64% | 50% | 80% | 62% | 80% | 64% |

Summary of Compared Data Between Fatal and Non-Fatal Cases with the Figures Used to Determine Significance" TABLE 16

| Poble No. | 100 | | Fatal | | | Non-Fatal | | | | |
|-----------|----------------------------------|-----------------|----------|-----------------------|-----------------|-----------|-----------------------|-------|-------------|---------------------------|
| anic ivo. | 1106 | No. of Cases | Means . | Standard Deviation | No. of Cases | Means | Standard Deviation | Value | P+ Value | Significant Difference |
| + | Age, race, sex W/M | 38 | 66.45 | 13.60 | 19 | 49.63 | 19.19 | 3.30 | 000 | |
| + | Age, race, sex W/F | 22 | 59.05 | 18.45 | 6 | 58.00 | 16.04 | 0.14 | >0 5 | No. |
| + | Age, race, sex C/M | 2 | 48.50 | 18.17 | 1 | 15.36 | 14.71 | 2 20 | 0.062 | |
| + | Age, race, sec C/F | 2 | 42.50 | 26.50 | 0 | - | 1 | 0.0 | 0.00 | 011 |
| 1 | Hospital days | 10 | 35.97 | 51.43 | 35 | 43.34 | 51.58 | 0.67 | >0 50 | 57 |
| 17 | Time between onset and diagnosis | 09 | 9.73 | 15.12 | 34 | 13.20 | 39.74 | 0.00 | >0.50 | N. Z |
| 6 | Pulse—before | 36 | 86.86 | 0.50 | 1 | 88 14 | 7.00 | 0.00 | 00.00 | No. |
| 6 | Pulse—during | 19 | 102.80 | 15.08 | 33 | 101.48 | 12.04 | 0.42 | >0.50 | 27 |
| 6 | Respirations—before | 33 | 21.45 | 10.50 | 0 | 22 56 | 4.47 | 080 | 0.45 | No. |
| 6 | Respirations—during | 61 | 26.79 | 17.86 | 3.5 | 26.75 | 619 | 0.00 | >0.50 | N. N. |
| 6 | - 1 | 26 | 99.81 | 2.22 | 0 | 10011 | 101 | 0.35 | 0.00 | S.Z. |
| 6 | Temperature—during | 51 | 101 06 | 2.45 | 31 | 101 79 | 1.48 | 1.48 | 017 | No. |
| 12 | Hemoglobin-before | 26 | 11.64 | 2.05 | 00 | 12.38 | 1 67 | 0.00 | 0.38 | 200 |
| 12 | Hemoglobin—during | 52 | 10.77 | 2.39 | 32 | 11.42 | 2.87 | 111 | 0.05 | 2 |
| 12 | WBC-before | 16 | 11.047 | 4.441.91 | 4 | 7.363 | 99.729 | 1.57 | 0.15 | N. Z |
| 12 | WBC—during | 53 | 19,758 | 11,175.1 | 30 | 15.381 | 8.964.81 | 18 | 0.08 | N. N. |
| 17 | Pmn-before | 14 | 74.79 | 88.28 | ~ | 70.67 | 10.96 | 0.66 | >0.50 | 7 |
| 17 | Pmn—during | 54 | 83.69 | 11.61 | 31 | 77.97 | 13.38 | 2.04 | 0.051 | No |
| 17 | NPN—before | 14 | 41.29 | 10.10 | IS. | 46.10 | 25.31 | 0.56 | >0.50 | No. |
| 12 | NPN-during | 44 | 50.77 | 28.97 | 22 | 31.50 | 74.46 | 30.2 | 004 | Ves |
| 77 | Sedimentation rate—before | 0 | Security | | 3 | 43.67 | 20.68 | 1 | 1 | 1 |
| 12 | e dui | 25 | 70.68 | | 16 | 81.69 | 34.42 | 0.92 | 0.36 | 10% |
| 17 | Albumin and globulin—Alb. before | 7 | 3,43 | | 1 | 1 | 1 | | 1 | 1 |
| | Alb. during | 26 | 2.72 | | 11 | 2.85 | 0.70 | 0.05 | >0.50 | N.O. |
| | Glob, before | 4 | 3.29 | | 0 | | 1 | 1 | 1 | |
| | | 26 | 3.68 | | 11 | 3.40 | 0.69 | 0.00 | 0.39 | S |
| 6 | Blood pressure—before systolic | 18 | 130.33 | | 9 | 126.17 | 6.01 | 0.51 | >0.50 | Z |
| | diastolic | 18 | 72.00 | | 9 | 75.67 | 8.60 | 0.53 | >0 50 | 2 |
| 6 | Blood pressure—during systolic | 45 | 126.78 | 26.70 | 22 | 124.41 | 23.08 | 0.65 | >0.50 | No. |
| | | 45 | 72.79 | | 22 | 71.73 | 10.79 | 0.35 | >0.50 | N. |
| 77 | Urine output—before | NO. | 1,267. | | 0 | 1 | 1 | 1 | 1 | |
| 71 | Urine outbut during | 2.4 | 1 4 2 7 | | 7 | 000 | 162 00 | | 2 0 | |

The formula used for difference of means was T value = $\frac{D}{\sqrt{N_1S_1^2 + N_2S_2^2}}$. $\sqrt{\frac{N_1N_2(N_1 + N_2 - 2)}{N_1 + N_2}}$. (From Hoel, P. G.: Introduction to mathematical statistics, Chapter 11, 2nd Ed., 1954, John Wiley & Sons, New York, p. 227.)

Prognosis: The mortality in this series of cases was 64% and did not change appreciably during the eight years of this study (table 15). Factors that might have influenced mortality were determined by comparing as groups the survivors and the fatalities (table 16). The only significant differences found between the two groups were that the patients who died were older and developed greater nitrogen retention during the course of their illness. Hospital infections were not significantly more lethal than those developed at home. Survivors were diagnosed, on the average, six days after onset, and fatalities were diagnosed eight days after onset, but analysis revealed this difference to be insignificant (P-value, > .05). The

Table 17

Mortality Rate of Bacteremia Due to Staphylococcus aureus

| Reference | Year | No. of Cases | Mortality | |
|------------------------------------|------|--------------|------------------------------|--|
| Lowenstein ⁸ | 1931 | 57 | 61 | |
| Dolman ²² | 1934 | 64 | 5.5 | |
| MacNeal and Frisbee ²³ | 1936 | 100 | 75 | |
| Rosenow and Brown ²⁴ | 1938 | 29 | 66 | |
| Scarpellino26 | 1939 | 187 | 91 | |
| Mandell ²⁶ | 1939 | 35 | 82 | |
| | | | Mean before antibiotics, 72% | |
| Harrell and Brown ²⁷ | 1941 | 44 | 63 | |
| Skinner and Keefer® | 1941 | 122 | 82 | |
| Spink and Wise28,29 | 1956 | 92 | 67 | |
| inland and Jones ²⁰ | 1956 | 196 | 45 | |
| Tze-Ying and Schu Chen10 | 1957 | 116 | 41 | |
| Wilson and Hamburger ¹³ | 1957 | 55 | 71 | |
| Schirger et al. ²² | 1957 | 109 | 34 | |
| octinger et an | | | Mean after antibiotics, 52% | |
| | | Total 1,226 | Mean of all cases, 63% | |

paucity of Negroes in this series has already been commented upon. The only associated diagnoses with an ominous significance were endocarditis and diabetes, in that death occurred in six out of eight and seven out of 12 such cases, respectively (table 6). There was a remarkable similarity between our mortality and that in the other large series of cases reviewed (table 17).

REVIEW OF LITERATURE

A complete bibliography and review of the staphylococcus has recently appeared, so we will mention only a few of the historical highlights of staphylococcic disease, and review briefly the papers in which a significant number of cases of staphylococcic bacteremia have been presented. Staphylococci were first noted in pus by Koch 17 in 1878, grown in liquid media by Pasteur 18 in 1880, shown to be constantly in abscesses by Ogston 19 in 1881, and thoroughly studied in 1884 by Rosenbach. Osler, 11 in the first edition of his text in 1893 describes "pyemia" as being caused by both staphylococci and streptococci. Some of his experience appears to have been

with staphylococcus bacteremia, since his descriptions might refer to cases reported in the present study.

In 1931 Lowenstein ⁸ reported on 18 cases of staphylococcus septicemia seen at the Jewish Hospital in St. Louis, and on about 29 cases in the literature. The mortality rate in these cases was 61%, and the most common portal of entry was lesions of the skin, such as carbuncles and furuncles. In a very lucid discussion of therapy, this author emphasized the importance of host factors, suggested blood transfusion as the treatment of choice, and particularly recommended transfusion with blood from a donor who had been given staphylococcic vaccine. He expressed skepticism regarding the use of gentian violet by vein, and also the use of bacteriophage. It is of some interest that the mortality rate of 61% with no specific therapy is almost identical to that achieved in our patients. Unfortunately, the age range of the patients treated was not given, so direct comparison of the mortality rates is not possible.

Dolman ²² in 1934 mentioned 64 cases of staphylococcal bacteremia who were treated with a staphylococcus antitoxic horse serum. Thirty-five (55%) of these patients died. The general remarks regarding the clinical pictures seen in these patients suggest that they were, in the main, very similar to those we have reported, and the five case reports showed the type of "dramatic response" to the antitoxin that we are accustomed to seeing today in sporadic case reports regarding therapy with antibiotics.

MacNeal and Frisbee ²³ in 1936 tabulated 100 cases of staphylococcic bacteremia that had been treated with bacteriophage prepared by themselves. The mortality rate was 75%, and a perusal of their tabulation and case reports suggests that the older patients died, and that, in general, the types of patients for whom they had supplied bacteriophage were similar to those we have reported.

Twenty-nine cases of staphylococcic septicemia were noted in 1938 by Rosenow and Brown.²⁴ They had a mortality rate of 66%, as compared with a mortality rate of 34% reported on 109 cases seen at the same clinic after 1940.³² An inverse relationship between age and prognosis was noted, as was the fact that death from staphylococcic bacteremia often occurred within four days of the onset of the disease.

Scarpellino ²⁵ in 1939 reported the compilation of 187 cases of staphylococcic bacteremia from hospitals in the Middle West, South and East, in which he found a mortality rate of 91%. He treated 17 cases with staphylococcic antitoxic horse serum, and eight of these survived. He found also that 28 children under the age of 18 months had a mortality rate of 78%, and felt that this denoted increased resistance in this age group.

Mandell reported in 1939 ²⁶ 35 cases of staphylococcus septicemia seen between 1929 and 1937 at Mt. Sinai Hospital in New York. The mortality was 82%; 30 patients had metastatic lesions; the skin and bones were the main portals of entry, and all of the diabetics (six) and patients with

meningitis (seven) died. He felt that the extremes of the white blood counts were of prognostic importance, because the patients with very high and very low counts died. The cases that survived usually did so by virtue of surgical intervention. The main differences in this experience and ours were the survival of some of our diabetics, and the fact that we failed to find significant prognostic value from the white blood count.

In 1941, in a discussion of the sulfonamide therapy of bacteremia, Harrell and Brown 27 mentioned 44 cases of staphylococcic septicemia. Their overall mortality was 63%, which is almost identical to that found in our present series. However, there was a mortality of 45% in the 27 patients

who received therapy with the sulfonamides.

One hundred twenty-two cases of staphylococcic bacteremia were reported by Skinner and Keefer in 1941.9 This experience closely paralleled ours in regard to material, and might be considered to be representative of the disease just before the advent of therapy with antibiotics. Their mortality was 82%, and the age of the patient was of the utmost prognostic importance in that only one patient over the age of 40 recovered, as compared to 24 recoveries in the over-40 age group in our series. The main portals of entry were the skin, respiratory passage, bones and genitourinary tract. Seventeen cases followed incision and drainage of an abscess or squeezing of a pimple. All of their nine patients with diabetes died, as did their four patients with bacterial endocarditis. Fever occurred in 83% of the patients, and chills in 25%. The majority of deaths occurred within 10 days of onset, and after that time the chance of survival increased. Five patients with primary pneumonia died. The sulfonamides were found to be of no help in therapy. The cases who survived usually did so when drainage of their original focus was possible. The most striking difference between our cases and those of Skinner and Keefer was the fact that 82% of their cases had metastatic lesions, whereas they were relatively rare among our patients. Apparently the antibiotics can prevent this complication, even if they do not always eradicate the disease. This was also found to be the case in Escherichia coli bacteremias.6 In addition, antibiotics also seem to increase the chance for survival of older patients and diabetics.

The mortality of cases of staphylococcic septicemia reported by Wise and Spink ²⁸ and Spink ²⁹ is of interest in that, of 92 cases seen, 59 died, which gives a mortality of 67%. Sixteen of the deaths occurred in 17 cases of acute endocarditis. More than half of these cases developed in the hospital, and some followed minor surgical procedures, such as skin incisions to establish intravenous infusions. Fourteen of 16 cases caused by penicillin-resistant organisms died. Bacteriophage studies of the 51 cases seen from 1951 to 1954 showed that their cultures were either in groups 1 or 2, or were nontypable. The more antibiotic-resistant strains were in phage type 3, but no correlation between phage type and virulence was found.

Finland and Jones 30 mention 196 patients who had coagulase-positive

Staphylococcus aureus in their blood in 1955 at the Boston City Hospital; of these, 89 died, a mortality of 45%.

The report by Collins et al. 31 of 16 cases of staphylococcic bacteremia in postsurgical cancer patients and in 23 patients with acute leukemia is hard to compare with other series because of the severity of the associated diseases. Their point of emphasis was that cannulations for intravenous infusion, and even finger pricks for the obtaining of blood samples, are important portals of entry for staphylococci in seriously ill patients.

One hundred sixteen proved cases of staphylococcic bacteremia were reported by Tze-Ying and Schu Chen in 1957. Eighty-five were males and 31 were females. The age range was from six months to 68 years. The primary focus was in the skin in 59 cases, and largely undetermined in the others. The patients all had fever, 37% had chills and mental confusion, 29% had skin rash, 29% had hepatomegaly and 17% had splenomegaly. Metastatic lesions were noted in 63% of the patients. Studies of the blood and urine paralleled almost exactly those found in the 100 cases reported in this paper. The gross mortality rate was 41%. Seventy-four per cent of the patients treated with penicillin survived. All seven patients over the age of 51 years died. This very excellent study was confirmed in all essentials in our patients. The difference in mortality can probably be attributed to the difference in ages between the two series of patients, since mortality of our patients under the age of 60 was 45%.

The report by Wilson and Hamburger 13 of 55 cases of staphylococcus septicemia seen at the Cincinnati General Hospital between 1940 and 1954 appeared to be paralleled in almost all respects by our study. Their over-all mortality was 71%, as compared to 64% in our series. They found age to be correlated directly with mortality. Sixty-four per cent (35) of their cases had endocarditis, and 60 per cent (23) of these survived. This is a better result with endocarditis than we achieved, in that six of our eight cases ended fatally. Admitting diagnoses, skin lesions and therapeutic results in general also were markedly similar in the two studies. We found more petechial hemorrhages in cases without endocarditis than did these Their discussion of therapy for the most part seems in agreement with our findings, since they emphasized that combinations of agents can be used without disadvantage, that organisms resistant in vitro rarely respond to therapy, and that the "management of this treacherous disorder continues to be one of the most challenging problems in the field of antibiotic therapy."

The report by Schirger et al.³² of 109 cases of staphylococcic bacteremia seen at the Mayo Clinic between 1940 and 1956 did not include cases of endocarditis, which may be one explanation of their mortality of only 34%. Metastatic complications were found in 12 of their patients, and these included pneumonia, epidural abscesses, septic arthritis, meningitis, osteomyelitis, pericarditis and mediastinitis. Forty-four of the cases followed operative procedures, most commonly transurethral resection. This is simi-

lar to our results, in that 22 of our cases appeared to follow operations, but greater than Skinner and Keefer's experience of in the pre-antibiotic era, when less than 10% of 122 cases developed after an operation. The comments of this group regarding treatment with antibiotics ("No antibiotic represents an automatic panacea for micrococcal bacteremia"), and the clinical picture presented by their patients, were very much in line with our experience.

The over-all comparison between the series of cases reported in the literature and those we have presented shows few fundamental differences. The types of cases seen by Osler in 1893 and by authors in the 1930's indeed seem to be very similar to the cases we have described. Individual case reports showed responses to blood transfusions, bacteriophage, antitoxic horse serum and to immune human serum that paralleled responses seen more recently to antibiotics. The main differences between the reports in the preantibiotic era and the more recent papers are that the numbers of older patients and of diabetics who survive appear to have increased, and that operative procedures now appear to be the cause of more infections.^{29, 31}

DISCUSSION

In an excellent review of factors concerned in the virulence of the staphylococcus, Elek ⁸³ has pointed out that "the factors which determine natural infectivity for man are still unknown." We will therefore consider briefly the triad of factors that make up any infectious disease, i.e., virulence, dosage and host resistance, and the implications of our data in regard to them.

Virulence: The significant factors in the virulence of staphylococci are unknown, although once the infection begins it is usually assumed that toxins play some role. The characteristics commonly associated with virulent strains, such as coagulase production, mannitol fermentation, and the production of alpha hemolysis, do not in themselves appear to play a significant role in the actual pathogenesis of staphylococcic disease. 34, 85, 36 Strains of staphylococci isolated from severe infections do not differ significantly from strains isolated from healthy carriers in regard to coagulase production, production of alpha hemolysis, toxin production or mouse virulence.^{2, 33} The one special characteristic of strains isolated from infections is that many of them throughout the world have been sensitive to certain bacteriophages, and it is not impossible that mouse virulence studies of phage types 80/81 or 44A might reveal factors that are related to virulence.37 The limited phage studies done on strains isolated from our patients would discount this possibility, however, because unknown as well as notorious phage types were indicted equally as the cause of severe staphylococcic infections.

Our data have not as yet revealed information regarding modes of virulence of the staphylococcus, but it is hoped that some information along this line may be found by the histologic study of the tissues of the 40 patients who were autopsied. At the bedside, the most striking evidences of toxicity were signs of myocarditis, which unfortunately were rarely established by electrocardiogram, and signs of an abnormal sensorium. Preliminary examination of the autopsy material has shown that actual physical invasion of the heart muscles, intestines, blood vessels and brain was an important factor in virulence.

Dosage: A large dosage of staphylococci may have been the cause of the infection in many of our patients, because they developed these infections in a hospital environment, which is now notorious for being the reservoir of large numbers of staphylococci. Approximately 50% of the personnel in the Milwaukee County General Hospital are staphylococcal carriers, and close contact between this personnel and patients undoubtedly resulted in some patients receiving a higher-than-usual dose of staphylococci. Methods of reducing the dosage of staphylococci within hospitals have been reported, and their general adoption may be expected to reduce staphylococci infections by reducing the dosages of this organism that hospitalized patients received. St. 30 Control of carriers within the hospital is still an essentially unsolved problem.

Resistance: It has been found in vitro that coagulase-positive staphylococci grow in human serum, and that in vivo phagocytes protect staphylococci from clearance from the blood stream. 40, 41 This would tend to discount the importance of circulating humoral or cellular factors as being important in the resistance to staphylococci. 40, 41 On the other hand, mucin will enhance the virulence of staphylococci in mice, and this acts by removing humoral factors from the serum; 42 and human gamma globulin will enhance the effectiveness of antibiotics against human and animal staphylococcic infections.43, 15 These findings tend to show that humoral factors may indeed play a role in resistance, even if in vitro systems of demonstrating this have so far not been devised. Organ resistance also seems to be a factor, as shown by the studies of Smith,44 who felt that "the ability of the staphylococci to grow in the human kidney may well be a contributing factor to the virulence of staphylococci in human patients." The significant rise in nonprotein nitrogen concentration found in our fatal cases was confirmatory of this concept.

The three positive findings in our study that may throw some light on factors of resistance in staphylococcic infection are the increase in mortality in the older age group, the possibly increased resistance of Negroes, and the higher levels of nonprotein nitrogen in the fatal cases. The negative finding that may be of some importance is the lack of differences between white cell response and temperature response in the fatal cases and in the survivors. The findings regarding age and race suggest a fruitful approach to the study of resistance in staphylococcal infections, since an investigation of phagocytosis, complement level, serum proteins, properdin activity and mouse protection antibodies in the serum of groups of individuals of differ-

ent ages and race might yield evidence in regard to the varying importance of these factors in resistance to this disease. The fact that temperatures and white cell elevations were not different in the survivors and in fatal cases might discount somewhat the importance of these factors in resistance to the staphylococci, and confirm in vitro studies that show that human phagocytes might act as a protection to staphylococci (table 16).41

It is hoped that a study of the tissues of the 40 patients in this series who were autopsied will reveal more information regarding the modes of virulence in this disease by showing which organs were most susceptible to

physical invasion or to toxins.

Treatment was manifestly unsatisfactory, and this will probably be the case until more information regarding both virulence and resistance is at This study might point out several things that may be fruitful in the management of severe staphylococcal infections that are based on consideration of virulence, dosage and resistance. Methods of combating factors of virulence are out of therapeutic range at present because they are not sufficiently well delineated. However, prevention of some infections would be possible if the dosage of organisms received by patients was reduced by closer control of carriers within hospitals, and by more meticulous care at the time of all operative procedures. In addition, if factors in resistance were augmented, the 55% chance of response that occurred in these cases of staphylococcic bacteremia when the proper antibiotic was administered might be increased. This fact has been recognized for a long time, in that blood transfusions have been suggested as therapy by several authors.8,9 Additional methods of accomplishing augmentation of natural resistance to staphylococci are indeed worthy of further investigation. Finally, the results of MacNeal 45 with bacteriophage and of Julianelle 46 with immune serum also might bear further scrutiny, for some of their patients seemed to do as well as did those treated with antibiotics.

SUMMARY AND CONCLUSIONS

One hundred cases of bacteremia due to coagulase-positive Staphylococcus aureus seen between 1951 and 1958 at the Milwaukee County General Hospital were presented. One-half of these developed while the patients were in the hospital for other reasons. Limited bacteriophage typing data revealed that staphylococci of a wide variety of bacteriophage types caused the infections. The most common portal of entry was on operative procedure (22%), followed by the respiratory tract (21%) and the skin (21%). The majority of patients were white males between the ages of 40 and 80. The most commonly associated diseases were pneumonia (20 cases), diabetes (12 cases) and endocarditis (eight cases). Seventy-four patients had an abnormal sensorium during the course of the disease, 57 had abnormal cardiac findings, and 45 had skin lesions. The spleen was palpable in 11 patients and the liver in 25; petechiae were seen in eight. Most patients were anemic and developed a leukocytosis. The only significant differ-

ences between the survivors and the fatalities were that the latter were older and developed greater nitrogen retention, but the two groups had similar febrile and white cell responses. Sixty-four of the patients died. Treatment was considered to be unsatisfactory because of the high mortality. Antibiotics to which the causative strains were sensitive (M.I.C., <6 µg./ ml.) were 55% effective, whereas no responses occurred when antibiotics were used to which the strains were resistant in vitro. Our most recent studies show vancomycin, neomycin, kanamycin and ristocetin to inhibit all strains of staphylococci, so one of these drugs should be used when the results of sensitivity studies are not available. Erythromycin, the tetracyclines and penicillin are probably as effective as the newer drugs against strains which show in vitro sensitivity to them. Prognosis did not improve during the years of this study, and early diagnosis did not significantly increase the chance of survival. Patients in the older age groups had a higher mortality. The mortality of staphylococcic bacteremia has not improved strikingly since antibiotics have come into use, although more older patients and diabetics survive. The most promising ways to reduce mortality are by preventing infection through reducing the dosage of staphylococci that patients receive while they are in the hospital, by increasing the dosage and specificity of antibiotic therapy, and by finding means to augment the natural resistance of individuals who contract the disease.

SUMMARIO IN INTERLINGUA

Es presentate 100 casos de bacteremia per Staphylococcus aureus a positivitate coagulasic, vidite inter 1951 e 1958 al Hospital General del Contato Milwaukee. Un medietate del casos se disveloppava durante que le patientes esseva hospitalisate pro altere rationes. Datos de lysotypia (non-systematic) revelava que un extense varietate de lysotypos bacterial habeva causate le infectiones. Le plus frequente porta de entrata esseva le sito de un intervention chirurgic (22 pro cento). Sequeva le vias respiratori (21 pro cento) e le pelle (21 pro cento). Le majoritate del patientes esseva masculos de racia blanc de etates de inter 40 e 80 annos. Le plus communmente associate morbos esseva pneumonia (20 casos), diabete (12 casos), e endocarditis (octo casos). Septanta-quatro patientes habeva un anormalitate del sensorio durante le curso del morbo, 57 habeva anormalitates in le constatationes cardiac, e 45 habeva lesiones del pelle. Le splen esseva palpabile in 11 patientes e le hepate in 25. Petechias esseva vidite in octo. Le majoritate del patientes esseva anemic e disveloppava leucocytosis. Le sol significative differentia inter le superviventes e le casos de morte esseva que le membros del secunde gruppo esseva de etates plus avantiate e disveloppava plus alte grados de retention de nitrogeno, sed le duo gruppos esseva simile in lor responsas de febrilitate e leucocytari. Sexantaquatro del patientes moriva. Le tractamento esseva considerate como non-satisfactori, viste le alte cifra de mortalitate. Le antibioticos al quales le racias causatori esseva sensibile (minimo del concentration inhibitori infra 6 µg/ml) habeva un efficacia de 55 pro cento, sed nulle responsa occurreva in le uso de antibioticos al quales le racias esseva resistente in vitro. Nostre plus recente studios monstra que vancomycina, neomycina, kanamycina, e ristocetina inhibi omne racias de staphylococcos. Assi un de iste drogas deberea esser usate quando le resultatos de studios de sensibilitate non es disponibile. Erythromycina, le tetracyclinas, e penicillina es probabilemente tanto efficace como le plus recente drogas in le caso de racias que exhibi sensibilitate a illos

in vitro. Le prognose non se meliorava durante le annos includite in iste studio. Le establimento precoce del diagnose non augmentava significativemente le probabilitate del superviventia. Patientes in gruppos de etate plus avantiate habeva un plus alte mortalitate. Le mortalitate ab bacteremia staphylococcal non ha descendite frappantemente depost que antibioticos esseva introducite in uso general, sed il es ver, un plus alte proportion de patientes in annos e de diabeticos supervive. Le plus promittente maniera de reducer le mortalitate es le prevention de infectiones per reducer le dosage de staphylococcos acceptate per le patientes durante lor sojorno al hospital, per augmentar le dosages e le specificitate del therapia antibiotic, e per trovar medios pro augmentar le resistentia natural de individuos qui contrahe le morbo.

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CLINICAL STAFF CONFERENCE

PRIMARY AMYLOIDOSIS: CLINICAL STAFF CONFERENCE AT THE NATIONAL INSTITUTES OF HEALTH*

Moderator: LUDWIG VON SALLMANN, M.D. Discussants: HERBERT E. KAUFMAN, M.D., GUNTER R. HAASE, M.D., FREDERIC C. BARTTER, M.D., and LOUIS B. THOMAS, M.D., Bethesda, Maryland

DR. LUDWIG VON SALLMANN: We have selected primary amyloidosis as our subject today for several reasons. In recent years a certain type of vitreous opacification has been recognized as being due to amyloidosis, with characteristics which distinguish this lesion from other types of vitreous opacities. Also, this form of vitreous change provides the opportunity to diagnose a systemic disease of protean symptomatology often undiagnosed during life. Finally, experts in this field are willing to participate in the discussion from other than the ophthalmologic viewpoint.

Dr. Herbert E. Kaufman has done considerable work in tracing members of families who have died with undiagnosed amyloidosis. He has also demonstrated the nature of the vitreous opacities on aspirated material. I should like to ask Dr. Kaufman to present the cases.

DR. HERBERT E. KAUFMAN: In our discussion of primary familial amyloidosis, we hope to emphasize several aspects of the disease.

First, opacities of the ocular vitreous occur in patients with this disease (figure 1). These resemble cotton-wool or glass-wool sheets when seen with the biomicroscope. Once the presence of amyloidosis is suspected, the diagnosis usually can be confirmed. These vitreous opacities, which often produce ocular symptoms early, can provide the necessary clue to the correct diagnosis.

Second, when the syndromes of primary amyloidosis are reviewed, it is apparent that, although the tongue, spleen and kidney are often the sites of microscopic amyloid deposits, clinically these organs are often normal and do not provide an indication of the presence or absence of amyloidosis. The presentation of several cases we have seen, and the discussions by Dr. Haase and Dr. Bartter, will cover some of the details of the clinical patterns encountered in patients with this disease. Dr. Thomas will review the pathologic anatomy of the cases we have studied.

Finally, the possible relationship of abnormal serum proteins to the ocular deposits and to the pathology of the disease will be considered.

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J. B. (00-19-69) is a 25 year old man who was referred to the Ophthalmology Branch with a chief complaint of cobweb opacities in the left eye and visual loss in the right eye. These ocular symptoms had begun in 1954 in the absence of pain or signs of inflammation, and initial eye examination indicated that a "perivasculitis" and vascular sheathing had preceded the opacities of the left eye. A presumptive diagnosis of uveitis had been made, although the search for a possible etiology was unrewarding. The past history was unremarkable except that in 1952 the patient had had hematuria for from one to two days, and had also had a 10-pound weight loss. Aside from this and his eye condition, he had been well.



Fig. 1. Drawing of the vitreous opacities as seen under the biomicroscope.

General physical examination revealed a thyroid nodule and palpable posterior cervical lymph nodes. X-ray examination revealed cystic areas of the carpal bones of the left hand. Clinically, the tongue, liver and spleen were normal, but a gastro-intestinal series suggested the possibility of slight hepatomegaly. Nonspecific ST and T wave changes were present in the electrocardiogram. The resected thyroid nodule and multiple biopsies contained amyloid, although a Congo red test showed only 27% retention.

During the last two years the patient has developed profound weight loss, neuropathy consisting of paresthesias as well as weakness and wasting of the hands, impotence, and bilateral "black eyes" in the absence of trauma. The neuropathy is striking and will be discussed by Dr. Haase. Impotence and weight loss occur fre-

quently and will be discussed in more detail. Although ecchymoses were not common in our patients, this sign is one of the typical manifestations of amyloidosis that may

suggest the correct diagnosis.

Since the patient had only light perception, vitreous transplantations were done in an effort to remove the opacities and to replace the opaque vitreous with normal donor vitreous. Only a slight and transient improvement of vision resulted. Examination of the diseased vitreous demonstrated that the opacities had the staining characteristics of amyloid. It seemed likely, therefore, that in being comprised of amyloid they were a specific and diagnostic manifestation of the disease. Although others in the family did not have the vitreous opacities, the patient's mother and half-sister had amyloidosis.

G. S. (A-56-17), the patient's sister, was a 35 year old housewife whom Dr. Bartter will discuss in some detail. Very briefly, gastrointestinal disturbances and a progressive neuropathy were present, causing debilitation and finally death. Similarly, this patient's mother, M. B., also had had amyloidosis, with progressive gastrointestinal disturbances, neuropathy, and ecchymoses of the lids, causing her death at the age of 38. Neither of these patients had macroglossia.

Vitreous opacities in cases of amyloidosis have been described previously, but the demonstration that they were comprised of amyloid so strongly suggested the possibility that they might be diagnostic of the disease that we recalled another unrelated patient who had similar opacities and who previously had been admitted to the Clinical Center because of his eye trouble.

J. S. (01-60-69) is a 78 year old man with opacities in the vitreous of the right eye since 1950. These opacities have become denser and have reduced the vision to little more than light perception; the vitreous of the left eye is relatively clear, and vision is 20/30. In 1957 he was admitted for the first time to the Ophthalmology Branch in good health. Because of the eye findings, a medical consultant at that time was asked to evaluate the patient as to the possibility of amyloidosis. On physical examination nothing could be found to support the diagnosis of amyloidosis. Biopsy was not done. Family history was noncontributory, the patient's older brother, T. S., having died of a "stroke."

The patient was recalled to the Clinical Center again in 1958 and, on the basis of the ocular findings, was admitted with a presumptive diagnosis of amyloidosis. This was confirmed by skin and muscle biopsy, by the properties of the vitreous removed during vitreous transplantation, and by the demonstration of an abnormality of the serum alpha-2 globulin on moving boundary electrophoresis. Reëxamination after the diagnosis was known revealed only a minimal proximal muscle weakness and occasional uncontrolled movements, consistent with senile chorea. The patient has since developed congestive heart failure and urinary difficulty, thought to be caused by prostatic hypertrophy.

Since the amyloid vitreous opacities had been seen only in the familial form of the disease, postmortem specimens were collected of the patient's brother, T. S. (A-58-190), who had died of a "stroke."

T. S. was 74 years old and had had numbness of one index finger in 1955. Fecal incontinence, nausea, vomiting and diarrhea developed in 1956. These necessitated hospitalization, but remitted to some extent. His coördination was poor. No liver or spleen was felt, but there were wasting of the muscles of the hands and legs, and loss of sensation and of reflexes in the legs. His pupils were large and poorly reactive. He developed fecal and urinary incontinence and difficulty in swallowing, and died of congestive heart failure.

The clinical diagnosis, made on the basis of the bizarre neuropathy, was intramedullary glioma, or motor system disease. The pathologic diagnosis on postmortem examination, in view of a small tongue, liver and spleen, had been diffuse arteriosclerotic vascular disease. Abnormalities of the vascular system were described.

In this case the family history as given by our patient was misleading, and the diagnosis of amyloidosis was missed both clinically and on postmortem examination. Dr. Thomas will discuss the large deposits of amyloid found in the blood vessels and elsewhere. If the disease had been suspected, the diagnosis would not have been difficult. The vitreous opacities of the brother, J. S., provided the first clue as to the nature of the disease in the case of T. S., where the diagnosis was otherwise not considered. The finding of such a case suggests that the disease may be more common than is suspected at the present time.

A third family was discovered when L. K. (00-90-07), a 61 year old man, was referred to us because he had become blind by vitreous opacities which appeared to be similar to amyloid opacities. For 12 to 13 years, vision had generally decreased in his right eye, and for five to six years the left eye had been similarly affected.

Vision in the right eye was limited to hand movements at 2 feet and in the left eye to hand movements at 6 feet, both with accurate light perception. Two biopsies of the skin showed minimal metachromatic staining material, but only in the gingival biopsy was sufficient material present for a definite prognosis of amyloidosis. Amyloid was present in the vitreous.

E. K., this patient's 60 year old brother, has had chest pain radiating to the shoulders for two years, and roentgenographically demonstrable densities in the left lung. Tuberculosis has been ruled out by negative tuberculin test and multiple gastric aspirations.

I. K., a 59 year old brother, has had chest pain as well as paresthesias in the arms and legs and aching of the stomach upon exertion for one to two years. Recently he has developed paresthesias, weakness, and slight wasting of the left hand.

B. K. (S-58-1915), a 51 year old brother, has had poor vision of his right eye, apparently related to birth trauma, and bouts of syncope believed to be on a cardiac basis.

A single skin biopsy has been done on B. K. and is negative for amyloid. I. K. and E. K. would not permit biopsies, but the densities seen on chest x-ray are similar to those seen in M. B. These, along with the appearance of neuropathy, suggest that others in the family may be suffering from amyloidosis, although without histologic proof the diagnosis is uncertain.

Several other patients also have been seen in the eye clinic.

E. K. (02-06-99) is a 61 year old woman with wasting of the hands, sclerodermalike changes of the skin on her hands, and amyloid vitreous opacities. (The diagnosis was confirmed by biopsy.) Her daughter had an early carpal tunnel syndrome but no eye abnormalities. A third patient, G. F., is a 61 year old woman (a cousin of E. K.) with congestive heart failure and amyloid vitreous opacities. It is of interest that the medical house-officer who initially examined this patient thought that the opacities in the eyes were due to cataracts.

Once a diagnosis of amyloidosis is suspected, it is often easily confirmed. I have attempted to present briefly the highlights of the findings of several patients we have seen. Though the syndromes are variable, certain patterns appear to be rather typical. The eyes are not affected in all patients with familial amyloidosis, and it is not established definitely that amyloid vitreous

occurs only in the familial form of the disease. However, the vitreous opacities of amyloidosis are typical, and may provide for a correct diagnosis not only in the patient under study but also in members of the family having no ocular manifestations. If such a clue is overlooked, the diagnosis can be missed.

Dr. Ludwig von Sallmann: Dr. Gunter R. Haase will present the

neurologic manifestations of familial amyloidosis.

DR. Gunter R. Haase: Nervous system involvement is quite common in primary amyloidosis, but it appears to be rare in the secondary form. The incidence of nervous system involvement in a series of 154 patients with primary amyloidosis has been given as approximately 15%. It appears to be distinctly higher in the familial form, and certainly the three patients seen by the Neurological Service belong in that category.

The first patient, J. B., had motor weakness and wasting of the muscles of his right hand for approximately one year, beginning four years after the onset of his disease. He had severe pain and a burning sensation in his hand and in both lower extremities, particularly at night. His voice had become progressively

hoarse, and he had shown a recent decrease of potency.

On examination he was found to have mild wasting in the muscles of the right forearm, and severe wasting in the right thenar and hypothenar eminences. There was mild weakness in the proximal muscles of both upper extremities, in all muscles innervated by the median nerve on the right and, to a lesser degree, in those supplied by the ulnar nerve. There were no fasciculations; his reflexes were normal. There was reduction of sensation in all modalities in the right arm, most prominent in the distribution of the median nerve. Pressure over the transverse carpal ligament produced no pain.

The second patient, referred to by Dr. Kaufman as E. K. (02–06–99), a 61 year old female, had had severe pain in her hands eight years previously, followed by progressive numbness. In addition, she had noticed wasting in both thenar eminences. At the time of examination there was pronounced bilateral wasting of the thenar eminences, and a marked sensory change on the palmar surface of the thumb and of the first two fingers of both hands. The skin over

the distal phalanges was smooth, hide-bound and shiny.

The third patient, previously referred to as J. S. (01–60–69), a 78 year old man, was referred because of involuntary movements. On examination, a very slight bilateral ptosis was noted. He had irregular writhing movements of his tongue and of the fingers and wrists of both hands, as well as shrugging, choreiform movements of the proximal upper extremities. He also had a moderate

degree of proximal weakness in both extremities.

The neurologic changes described in the first two patients are in accord with those reported in the literature. These alterations can be brought under the common denominator of involvement of peripheral nerves or of the dorsal root ganglia by amyloid deposits. The peripheral nerve, the dorsal root entry zone, the dorsal root ganglion, the autonomic ganglion and the meninges are the areas most commonly involved. Kernohan and Woltmann² believe that the neuropathy accompanying primary amyloidosis is due to occlusion of nutritional vessels of the nerves. This may be true in some instances, but in other cases deposition of amyloid occurs between the fibers of the nerve. In certain instances the amyloid is deposited between the fibers of the peripheral nerve and within skeletal muscle, thus leading to atrophy of neighboring fibers. Such

deposits are thought to be responsible for the proximal muscle weakness in the third case reported here. This case had shown evidence of muscular involvement in addition to the marked chorea. Whether the chorea can be attributed to the amyloidosis is uncertain. We consider it to be the senile form.

Muscular involvement has been described in many cases in the literature. There is a suggestion that this involvement occurs more prominently in proximal muscles and in the muscles of the trunk. In one case in the literature, myotonia has been diagnosed, although the description given makes this seem implausible.

It is generally stated that the central nervous system remains unaffected in primary amyloidosis. This is true only conditionally. Involvement of the choroid plexus by amyloid deposits is a fairly common event.

Similar deposits can be seen in blood vessels in other areas of the brain. Such vascular changes have been held responsible for the granular cortical atrophy seen in some cases of primary amyloidosis. A few cases are also reported in the literature where material with the staining characteristics of amyloid was seen in plaques within the parenchyma of the central nervous system. Clinically, these patients presented presentle dementias. However, in no other organs of the body were amyloid deposits seen in these cases, and certainly their relation to the disease under discussion is highly dubious.

The same must be said for some cases of alleged amyloid tumor-like deposits within the brain. Certain psychiatric changes of a depressive or agitated psychotic nature have been described in primary amyloidosis, but, once again, their relation to the primary disease is uncertain.

With the pathology of the peripheral nerve accepted, the inquiry must be directed toward the nature of involvement. In some cases we can find peripheral nerve involvement of the type seen in toxic or nutritional disorders. In these disorders the involvement will begin peripherally, accompanied by wasting, reflex and sensory changes, and trophic disturbances.

Another possible form is that of a mononeuritis multiplex, that is, involvement of larger nerve trunks, producing sensory changes and muscular wasting in the area innervated by the nerve. The nerve itself in these instances may be thickened and tender to pressure.

Involvement of the autonomic nervous system may become manifest by diarrhea or constipation, by disturbance of the sphincters, and by impotence. The cranial nerves have been reported to be involved in some instances.

The spinal fluid will show abnormality in some cases, increase of the protein and alteration of the gold curve being the most prominent findings. As has been stated earlier, involvement in the familial forms is considerably greater than in the sporadic forms of primary amyloidosis. In 1952 Andrade ⁸ published in *Brain* a series of 74 cases occurring in 12 pedigrees of Portuguese origin. All of these lived within a well defined area of the country. The disturbance manifested itself by a paresis in the extremities, particularly the lower ones; by early impairment of sensation; by intestinal disorders; by disorders of sphincter functions, and by impotence. Pupillary changes were also common in these patients.

At autopsy, two of these patients showed an extensive involvement of internal organs by amyloid deposits. Some of them were reported to have shown perforating ulcers of the feet. Similar ulcers of the feet have been seen among members of the family reported by Denny-Brown 4 under the heading, "Hereditary Sensory Radicular Neuropathy." In this family the affected mem-

bers had recurrent ulcers of the feet, sensory disturbances, lancinating pain and nerve deafness. Amyloid deposits were seen in the dorsal root ganglia, with degeneration of the ganglion itself. There were no amyloid deposits elsewhere, and the relationship of this disorder to the other cases of primary amyloidosis is not clear.

In summary, it may be stated that the peripheral and the autonomic nervous system show a fairly frequent occurrence of disturbance in primary amyloidosis, and this disease must be strongly considered in the differential diagnostic possibilities of chronic neuropathy in adult life, particularly in the familial form.

DR. LUDWIG VON SALLMANN: Dr. Frederic Bartter has kindly consented to discuss some of the systemic manifestations of the patients described by Dr. Kaufman.

DR. FREDERIC C. BARTTER: The diagnosis of amyloidosis by the internist is often difficult.

Our experience with this disease may best be described perhaps by telling you about patient I. B., to whom Dr. Kaufman has already referred. J. B. was admitted because of an obscure eye condition, and the obscurity persisted for quite a time. During this period it was suggested that he might benefit from steroid therapy. Since we were studying steroids, we admitted him as a "normal control" on this study.

In turn, our studies were deferred because of the necessity of removing an enlarged thyroid, which, as you have heard, was found to be composed mostly of amyloid. At this point it developed that the patient had a sister with a syndrome that was being studied extensively at the Johns Hopkins Hospital. This patient was admitted with a history of having had shooting pain in her toes and heels for four to five years, of having had a weight loss of 40 pounds, a feeling of tiredness and exceeding weakness for two years, and amenorrhea for almost two years. The immediate cause of her hospitalization was diarrhea, constipation, nausea, and vomiting, and there was a history of having had episodes of nausea and vomiting for the previous 18 months. These were so severe as to require frequent hospitalization for dehydration. The medical record revealed a story of blurring of vision for one year, of hematuria starting seven months previously, of numbness in her legs and fingers, memory loss, dizziness, and marked bruising of her buttocks for the last five to six months.

Studies at the Johns Hopkins showed that the patient did not have fever, but did have tachycardia and marked postural hypotension. Her skin was dry, and she had irregular pupils which did not react to light or accommodation. The changes Dr. Kaufman described were not seen in her eyes. Her spleen was enlarged, but her liver was not. Very marked muscle wasting accompanied her weakness. She had bilateral foot drop, and was known to have absent pain sensation in her lower extremities. Deep tendon reflexes were absent as well.

Many laboratory tests were done. She had anemia, and had no free acid with histamine. Cephalin flocculation was positive, and the cerebrospinal fluid protein was very high.

On her first admission a biopsy of muscle was done which was said to show chronic vasculitis. The patient left the hospital for a period, to be re-admitted somewhat later. At this time she was emaciated, and several new biopsies confirmed the diagnosis of amyloidosis.

However, many diagnoses had been considered previously. Some of those

which were ruled out by studies at the Johns Hopkins Hospital were tabes dorsalis, periarteritis nodosa, disseminated lupus erythematosus, vasculitis, carcinomatosis and sarcoidosis. At her second admission, the similarity of her syndrome to that of the worst of the 74 cases described by Andrade ^a had become apparent. It was also during this second stage that her doctors learned of the amyloid disease in her brother.

It then became of considerable interest to pursue her family history. Her mother, M. B., had died at an early age of a syndrome strikingly similar to that from which she herself was dying. The mother had not been autopsied. There was one biopsy, however, that had been done because her syndrome had been so obscure. She had been admitted with a story of fatigue, weakness and diarrhea, with a weight loss of 30 pounds, dizziness, and numbness and aching of her legs. Immediately before her studies were begun in the hospital in Virginia, she was bedfast. There was decreased urinary output, blood in her urine, and a history of prominent bruising.

These studies indicated the following: The patient, M.B., had had fever, tachycardia, and very low blood pressure. Her skin was dry and inelastic, and had shown numerous ecchymoses. She had had sluggish pupillary reflexes. There was enlargement of both liver and spleen. Cephalin flocculation was positive, there was very marked anemia, and laboratory studies were otherwise not diagnostic. X-ray showed scattered pulmonary calcifications, a finding to which Dr. Kaufman referred. Tuberculin test was negative, and x-rays showed what was termed segmental ileitis. An electrocardiogram showed low amplitude in all leads. Skin and muscle biopsies were done. The diagnoses entertained for this patient were pernicious anemia, thrombocytopenic purpura, aplastic anemia, malignancy, polyposis, subacute bacterial endocarditis, periarteritis nodosa, and lupus erythematosus disseminatus. The only remaining bits of evidence in her case were a slide and a block that remained from the biopsy. The slide was first reviewed by a pathologist who considered the findings to be not specific, but later examination of the slide showed abundant amyloid in the skin.

The presence of familial amyloidosis in these three members of a family led to an extensive search of the entire family history by Dr. Lawrence Shulman, of Johns Hopkins. Thus far, this particular family has not shown any other clear-cut cases.

Dr. Ludwig von Sallmann: We are very fortunate to have Dr. Louis Thomas talk to us about the general pathology of familial primary amyloidosis.

Dr. Louis B. Thomas: Amyloid, microscopically, is an extracellular, homogeneous hyaline substance which stains metachromatically with methyl violet. The diagnosis is made on the basis of its appearance and metachromasia in histologic sections.

Many textbooks refer to the differences in pattern of distribution of amyloid in primary and secondary amyloidosis. It is common knowledge that the greatest amount, and favorite location, as it were, of amyloid deposits in secondary amyloidosis are in the liver, spleen, kidneys and adrenal glands. In primary amyloidosis the substance may be found in any organ or tissue, but most frequently deposited in the heart, blood vessels and other mesodermal structures. However, amyloid may be found in many different organs and tissues in both primary and secondary amyloidosis. The following data give the sites of amyloid deposition in 38 patients studied by Dahlin 5 in 1949. He found

amyloid in the spleen in each of 30 patients with secondary amyloidosis, and in each of eight patients with primary amyloidosis. His data were based upon histologic examination of sections of these tissues. The kidneys, adrenal glands, liver and lymph nodes were more frequently involved in secondary than in primary amyloidosis. Other organs, such as the pancreas, prostate gland, thyroid gland, gastrointestinal tract, heart, lungs, skeletal muscle and nerves, were more frequently involved in patients with primary amyloidosis. The point to be stressed is that many organs and tissues are involved in most cases of both secondary and primary amyloidosis. Therefore, the presenting symptoms of patients with amyloidosis may vary considerably.

Table 1

Amount of Amyloid in Various Organs and Tissues

| | 0 | |
|---------------------------------|--------------|-----------------------|
| | G. S. (35 9) | T. S. (74 8) |
| Spleen | ++++ | + |
| Kidney | ++ | + |
| Adrenal glands | +++ | + |
| Liver | + | ± |
| Lymph nodes | (N.S.)* | + + ± (N.S.) |
| Pancreas | +++++ | + |
| Prostate gland | | (N.S.) |
| Thyroid gland | +++++ | (N.S.) |
| G. I. tract | ++++ | (N.S.) |
| Heart | ++++ | ++++ |
| Lung | + | ++ |
| Skeletal muscle | ++++ | (N.S.) |
| Nerves | ++++ | (N.S.) |
| Uterus | +++++ | |
| Urinary bladder | ++++ | (N.S.) |
| Bone marrow | + | (N.S.) |
| Pituitary gland | ++ | (N.S.) |
| CNS (dura and cerebral vessels) | ++ | ++ |
| Testes | | (N.S.) |
| Parathyroid glands | (N.S.) | (N.S.) |
| | | |

^{*} N.S.: no sections available for study.

You have heard Dr. Kaufman describe the different symptom-complexes observed in patients with familial primary systemic amyloidosis. Their symptom-complexes correlate quite well with the amount of amyloid found in the various organs (table 1). Patients G. S. and T. S. are members of two of the family groups who had familial primary systemic amyloidosis described by Dr. Kaufman.

T. S., the patient from New Jersey, died of intractable heart failure. He was found to have extensive deposits of amyloid in the heart, and only minimal deposits of amyloid in other organs and tissues (table 1). It should be mentioned that the heart is frequently involved in primary systemic amyloidosis, and, in fact, there are several reports of patients who had amyloidosis entirely confined to the heart. Amyloid may be heavily deposited in the endocardium, so that one can recognize the disease grossly in the autopsy room by observing glistening specks of amyloid in the endocardium of the atrium. The endocardium and myocardium in this patient were greatly thickened due to amyloid.

G. S., the patient described by Dr. Kaufman and Dr. Bartter, is the halfsister of J. B., the patient who is still living and who was first observed to have amyloid in the vitreous. G. S. had a long chronic illness, characterized by symptoms related to nearly every organ system. At autopsy there was a large amount of amyloid in nearly every organ and tissue (table 1). Every section from the tongue, esophagus and all portions of the gastrointestinal tract showed some amyloid. The gastric mucosa was irregularly infiltrated, and the reddish stained amyloid had produced so much atrophy of the gastric mucosa that the sections could scarcely be recognized as stomach.

The degree of atrophy of the pancreas produced by amyloid in this patient was scarcely believable. The pancreatic lobules were in general of normal size and shape and there were a normal arrangement and distribution of ducts and vessels, but cellular structure of the pancreatic lobules was almost entirely replaced by amyloid. In fact, the only acinar epithelial elements which remained were a few clusters of detached and disorganized epithelial cells.

The ovaries of this patient were also severely atrophic, and every vessel in the cortex and medulla was thick-walled due to amyloid deposition. Occasional corpora albicantia could be seen, but no Graafian follicles or ova were found. The pituitary gland, though not markedly atrophic, had moderate amounts of amyloid in all the vessels. Deposits of amyloid were found in the thyroid gland, with atrophy of thyroid follicles. You will recall that J. B., the half-brother of this patient, presented with an amyloid goiter. As can be seen in table 1, many other organs and tissues contained large amounts of amyloid.

The purpose of presenting the pathologic data of these two patients was to show how widespread amyloid usually is in people with primary systemic amyloidosis, and also to show that the patient's symptoms can be correlated with the amount of amyloid in particular organs and tissues.

Dr. Ludwig von Sallmann: Dr. Herbert E. Kaufman will make some comments on pathogenesis.

Dr. Herbert E. Kaufman: Although amyloidosis was first described by Rokitansky ⁶ in 1842 and by Virchow ⁷ in 1855, knowledge of the pathology of the disease remains incomplete.

It seems likely that many different types of amyloid exist. The development of amyloid deposits in animals immunized for toxin production, and possibly in hypertensive humans, may be different from the deposits that appear on an inheritable basis. Similarly, the familial form of amyloidosis may have a different metabolic abnormality from the amyloidosis of myeloma, of chronic disease, or of localized amyloid tumors, even though the staining may be similar.

The familial form of primary amyloidosis was first demonstrated in 1950 by Ostertag.⁸ In 1956 an excellent review and experimental study on another family with this disease was reported in *Medicine* by Rukavina ¹ and his coworkers. In this family, these investigators demonstrated that approximately half of their cases with familial amyloidosis had an abnormal or poorly resolved alpha-2 globulin in the serum, as studied by free electrophoresis. The finding that 13 unaffected members, although younger, also had similar protein patterns, however, suggested the possibility that this abnormal serum protein might be an associated genetic anomaly in this one family, not directly related to the disease.

In the case of J. B., and later in T.S., we have confirmed the presence of abnormal alpha-2 serum fractions associated with familial amyloidosis (figure 2). These cases were unrelated to the family in the initial report, providing further evidence that the protein abnormality may be a specific manifestation of

the disease, and the result of an inherited metabolic defect of probable significance in its etiology. The hereditary pattern and demonstrable protein abnormalities lend a unity to this particular form of the disease, and suggest that mechanisms of pathogenesis in the familial forms may be similar.

Three major hypotheses concerning the pathogenesis of amyloidosis are presently popular. One, as put forth by Warren 9 and Reimann, 10 suggests that the deposition of amyloid is caused by a primary local "defect, perversion, or injury" of mesenchymal tissue or fibroblasts in the area of the amyloid deposits. A second holds that all amyloidosis is due to hypersensitivity and an antigen-antibody interaction. The third is that an abnormal non-antibody substance may be transported by the blood and somehow deposited as amyloid in the affected tissues.

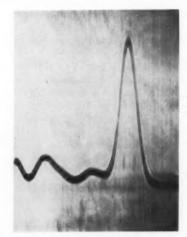


Fig. 2. On moving boundary electrophoresis of the serum, an abnormal peak was present in the alpha-2 globulin region.

The nature of the deposits in the vitreous body of the eye permits some insight into their pathogenesis. The normal vitreous is a gel that contains only a few cells at its surface. The abnormal vitreous obtained in our patients comes from the acellular portion in the center of the vitreous, and the opacities are removed only with great difficulty. They appear to be fixed in this central area, and cannot be washed out despite extensive lavage. When these opacities, which occur so far from the cellular elements, are stained for hyaluronic acid before being stained for amyloid, the normal vitreous fibers are stained blue. The hyaline metachromatic amyloid appears to be deposited on a framework of these blue fibers, as if the vitreous fibers acted as centers of crystallization or polymerization for the components of amyloid. This deposition of amyloid on vitreous fibers seems to explain the structure and stability of the opacities which did not permit removal despite extensive lavage.

It may be that the abnormal blood protein is a precursor of the amyloid deposits observed. At present, however, no information exists concerning this

hypothesis. Attempts to cause the deposition of amyloid on normal cadaver vitreous by incubating it with serum from patient J. B. have been unsuccessful. The occurrence of these deposits in an acellular area suggests, however, that the amyloid is a product of substances produced at a distance—perhaps in a remote organ such as the liver. The absence of signs of inflammation in our pathologic specimens indicates that this protein deposition is not an antigenantibody reaction in the usual sense.

Some cases of amyloidosis seen early in the disease show perivascular deposits in the retina as the first ocular sign. Similarly, systemic amyloid deposits appear to form first around the walls of capillaries, then around arteries, and finally on the surface of cells and on fine collagen and reticulum fibers. This perivascular and pericellular infiltration seems to be consistent with the hypothesis that it is the deposition of this substance around vessels and cells that leads clinically to the appearance of ischemic heart disease, ischemic neuropathy and granular degeneration of the brain, usually in the absence of obvious vascular occlusion, grossly or microscopically. Microscopically, it appears as if cellular nutrition is interrupted and the cells are infiltrated and replaced by the amyloid in the absence of inflammation or of tumor formation. The final appearance may be that of a tissue almost totally comprised of amyloid, but with the architecture basically undisturbed.

In the diagnosis of amyloidosis, the Congo red test has been used with variable results. Selikoff ¹¹ analyzed 1,000 Congo red tests in tuberculous patients, and his findings are rather typical. He concluded that 0 to 89% absorption was negative. Patients with 90 to 99% absorption often had amyloidosis, though this was not reliable, and patients with 100% absorption probably had amyloidosis. Cases have been described with 100% absorption where no amyloid was found on postmortem examination, and many cases are described with amyloidosis, but with a negative Congo red test. In addition, death, coma, hemiplegia and a disfiguring red staining of cutaneous amyloid deposits have been reported after Congo red injection, even in cases with no previous history of Congo red tests.

As Dr. Thomas has pointed out, the most important diagnostic test is biopsy. Almost any tissue may be biopsied. The skin, gingiva and liver are the most commonly used. Amyloid cannot be found as a rule by bone marrow aspiration. Attempted biopsy of a sago spleen may lead to splenic rupture.

There is no recognized therapy for amyloidosis. In experimental amyloidosis, castration and thyroidectomy are harmful. Since, clinically, testicular function and thyroid function are often below normal, replacement therapy might be of value.

In summary, the appearance of amyloid vitreous seems to be diagnostic, and may occur only in the familial form. Cases have been reported of primary amyloidosis where the vitreous opacities were the only sign suggesting the diagnosis. The tongue, liver, kidney and spleen are often clinically normal in patients with this disease. Common clinical syndromes have been illustrated by several case reports.

The presence of an abnormal serum alpha-2 globulin has been confirmed, and the possible importance of this protein in the etiology of the disease and the formation of amyloid vitreous is discussed.

Dr. Ludwig von Sallmann: Dr. Kaufman has summarized this conference on familial amyloidosis. Before I ask for comments and questions, I would add one point which I think might explain why the therapy from the ocular viewpoint—that is, lavage of the vitreous—is so ineffective.

It was one of the outstanding American ophthalmologists, Dr. F. H. Verhoeff ¹² in Boston, who, about 30 years ago, said that if we were able to liquefy the vitreous by any therapeutic means we could improve the treatment of vitreous disease. Were we able to liquefy the vitreous in familial amy-

loidosis, we could wash it out, but as it is, we cannot.

I might add that many experiments have been carried out to bring about the liquefaction of vitreous by using various types of proteinases, collagenases, hyaluronidases, and surgical means. None of these procedures was successful in producing a liquefaction of the vitreous, either in experimental animals or in isolated vitreous preparations.

Are there any questions?

QUESTION: The discussants have not revealed the chemical nature of amyloid—whether it is a glycoprotein, or protein at all—or how much glucosamine it contains. Have hyaluronidase and various other mucolytic agents been tried? Do such things produce disintegration of the intracellular mucopolysaccharides of the eye? Has chemical evidence of this nature been interpreted?

DR. LUDWIG VON SALLMANN: Dr. Kaufman, do you want to answer?

Dr. Herbert E. Kaufman: Our knowledge of the composition of amyloid is as yet very incomplete. One of our cases of primary amyloidosis of the nonfamilial type has been analyzed chemically as follows: water, 76%; nitrogen, 12.5%; hexose amines, 1.11%; neutral sugars, 3.7%; and uronic acid, 0.45%. This is similar to the reports of Hass 13 on the analysis of amyloid from patients

with the secondary amyloidosis of chronic tuberculosis.

In our hands, the staining characteristics of both the systemic and ocular amyloid are not altered by hyaluronidase, although the blue staining of the vitreous fibers is abolished. In addition to that, experiments with Dr. Sam Spicer have been done with neuraminidase and sialidase, and have revealed no apparent alteration in staining properties. If sialic acid and neuraminic acid are present in amyloid, they do not seem to be responsible for the metachromatic staining properties, and add little to the understanding of the deposition and staining of the substance.

All of this is negative evidence. It seems that a profitable approach might be to try to establish an identity between the circulating serum components and

the amyloid deposits; immunologic technics may make this possible.

Dr. G. MILTON SHY: I am interested in one further comment on the deposition of amyloid in the pure amyloid and the multiple myeloma. In Dr. Kaufman's observation of patients with myeloma, the vitreous opacities were not described, to my knowledge.

DR. HERBERT E. KAUFMAN: Dr. Thomas, I think, could better comment

on the pathology.

Dr. Louis B. Thomas: I have seen a few deposits of amyloid in patients with multiple myeloma, and I have been shown sections in which it was believed the myeloma cells contained this material. I do not have any information about the chemical differences between the amyloid-like material in multiple myeloma and that observed in these patients with systemic amyloidosis.

SUMMARIO IN INTERLINGUA

Es revistate le aspectos clinic de amyloidosis primari per le ophthalmologo, le neurologo, e le internista; le pathologo revista le histologia del morbo. Le discussion se concentra super le observation de vitrose opacitates que possede characteristicas structural de valor diagnostic e que es identificate histochimicamente in extrahite specimens de fluido vitrose como depositos amyloide. Es digne de notitia que inflammatori signos ocular es absente e que disturbation del vision resultante de alterationes vitrose es possibilemente un precoce symptoma de presentation. Viste le complexitate del signos neurologic e visceral del morbo, resultante in difficultates diagnostic, le examine biomicroscopic del oculo pote in certe casos provider un importante indice orientatori in le recognition del disordine systemic. Observationes facite usque al tempore presente suggere que amyloide opacitates vitrose occurre principalmente, si non exclusivemente, in le typo familial de amyloidosis primari.

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CASE REPORTS

RHEUMATOID AORTITIS: REPORT OF AN UNUSUAL CASE *

By Peter Hope-Ross, M.B., Ch.B., Edward J. Bien, M.D., Vincent S. Palladino, M.D., and Gilbert Graham, M.D., Hempstead, N. Y.

WITHIN recent years there has been increasing evidence that rheumatoid arthritis is a systemic disease with widespread visceral manifestations. Much interest has been focused on the cardiovascular changes occurring in patients who exhibit spondylitis and the articular manifestations of rheumatoid arthritis.¹⁻¹²

The cardiac pathology that occurred in many cases of rheumatoid arthritis manifested itself as a pancarditis, and because the valvular endocarditis often simulated that seen as a sequel of rheumatic fever, the changes were originally interpreted as rheumatic in origin. 16, 10, 11 On this basis it was concluded that rheumatic heart disease was more common in patients with rheumatoid arthritis than in the general population. In several series of patients with rheumatoid arthritis the incidence of so-called rheumatic heart disease has varied from 15 to 56%, which suggested to several authors that the two diseases were related in some way. 1, 6, 9, 10, 11 Of late, however, there has been increasing evidence that rheumatoid carditis and rheumatic carditis are different entities. 12

We have had the opportunity of studying a patient in whom the diagnosis of rheumatoid arthritis was definitely established and who went into spontaneous remission. Remission was later followed by symptoms of aortic incompetence and x-ray evidence of progressive aneurysmal dilatation of the root of the aorta. It is interesting to note in passing that, in one series of 100 cases of aortic insufficiency, five showed evidence of rheumatoid spondylitis. We consider that in our case the basis for the aortic aneurysm is rheumatoid cardiovascular disease, and because of the rarity of the condition are prompted to report it in detail.

CASE REPORT

The patient was a 42 year old male psychologist who was said to have had "growing pains" during childhood. When he was 16 years old a cardiac murmur was heard. However, he had no limitation of activity, and in college participated in varsity sports. He was commissioned in the Army of the United States in 1942, and physical examination at that time was normal. In 1946, while still in the Army, the patient developed polyarthritis associated with pain, swelling and redness of multiple joints, including the proximal interphalangeal and metacarpal joints of the hands, and the elbows. Persistent subcutaneous nodules appeared. Histologic diag-

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nosis of one of the excised nodules was "rheumatoid subcutaneous nodule." At this time the patient had no heart murmurs, and there was no cardiac enlargement (figure 1). He received a medical retirement from the Army because of rheumatoid arthritis and was pensioned.

In 1949, minimal cardiac enlargement and aortic dilatation were noted on routine x-ray examination (figure 2). These findings had progressed considerably by 1952 and were quite marked by 1953 (figures 3 and 4); at this time a diagnosis of rheumatic heart disease with aortic insufficiency was postulated. There was then complete remission of the rheumatoid arthritis and no residual deformity. In 1953, the patient's laboratory work-up included Mazzini, Kolmer's, Kahn and New York State microflocculation tests, all of which were negative. The result of the serologic test

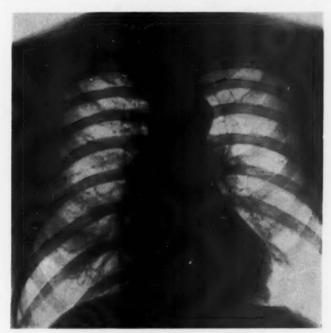


Fig. 1. Chest x-ray, 1946.

for syphilis as performed with the Venereal Disease Research Laboratory (VDRL) antigen was also negative. On direct questioning he denied ever having lues, a positive test for the disease, the symptoms of lues or of any other venereal disease. In December, 1954, the patient was treated with Tapazole because of clinical signs of hyperthyroidism, tachycardia uncontrolled by digitalis, and a 24-hour I¹³¹ uptake of 64%. There was good clinical response.

In January, 1955, a 3 mc. dose of I¹⁸¹ was administered in an attempt to reduce thyroid hyperfunction permanently. Four additional millicuries were given in March of the same year. Approximately two weeks following the administration of each dose of I¹⁸¹ the patient developed thyroiditis. Tapazole, 30 mg. daily, was administered for about one month post-therapy on both occasions. Medication with Tapazole was continued intermittently for many months.

In June, 1955, investigation at Mount Sinai Hospital in New York City revealed a euthyroid state. Despite this, the patient continued to take Tapazole without medical advice, since he felt better when on the drug. A few months later it was noted that moderate anemia without leukopenia had developed; this was considered possibly to be due to Tapazole, since the anemia was less severe when the medication was discontinued.

Examination at about this time revealed a chronically ill adult white male. Ears, eyes, nose and throat were negative except for pallor of the mucous membranes and arteriolar pulsations on retinoscopy. The heart was enlarged to the left, with the point of maximal impulse in the sixth interspace at the anterior axillary line. There

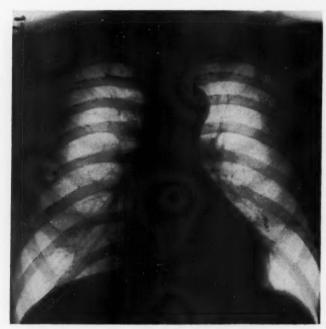


Fig. 2. Chest x-ray, 1949.

were a systolic and a short diastolic murmur at the apex and a grade III diastolic murmur in the aortic area. The apical rate was 140 per minute and regular. The blood pressure was 142/70 mm. of Hg. The lungs were clear. The liver was palpable one fingerbreadth below the costal margin. There was no edema of the ankles. Fluoroscopy confirmed enlargement of the left ventricle and showed gross dilatation of the aorta. An electrocardiogram showed sinus tachycardia and indicated left ventricular hypertrophy. The impression as to the diagnosis at this time was aortic insufficiency, with marked aortic dilatation of either rheumatic or rheumatoid etiology. The patient continued in moderately good cardiac compensation while being maintained in a hypothyroid state with Tapazole, but he finally became decompensated, and in December, 1955, was admitted to Bronx Veterans Administration Hospital with irregular tachycardia and moderately severe congestive failure.

While in the Bronx Veterans Administration Hospital the patient's heart rate became regular at 96 per minute, due to the establishment of a sino-auricular nodal rhythm with primary heart block.



Fig. 3. Chest x-ray, 1952.

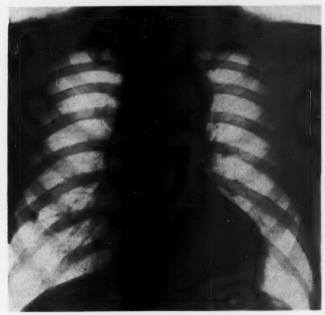


Fig. 4. Chest x-ray, 1953.

The patient was admitted to Meadowbrook Hospital for the first time on December 16, 1955, immediately after his release from the Bronx Veterans Administration Hospital. He was in severe cardiac failure. X-ray at this time showed great enlargement of the heart, mainly in the region of the left ventricle, with marked dilatation and tortuosity of the aorta (figure 5). His condition deteriorated despite therapy, and he died on December 21, 1955.

Autopsy Report: Autopsy was performed within six hours of death. Except for hepatomegaly, ascites (1,500 c.c.) and perithyroidal fibrosis, the pertinent findings were limited to the thorax. The heart occupied more than one third of the thoracic cage, the apex resting against the left costal border in the midaxillary line (figure 6).

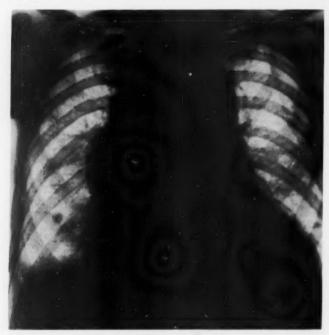


Fig. 5. Chest x-ray, 1955.

There was a pericardial effusion of approximately 50 ml. of clear, watery, amber fluid. The heart weighed 650 gm. The valve circumferences were: tricuspid, 14 cm.; pulmonary, 8.5 cm.; mitral, 12 cm.; aortic, 13.5 cm. The wall of the right ventricle was 0.2 to 0.6 cm. thick; the wall of the left ventricle was 0.8 to 1.5 cm. thick. Both atria and their auricular appendages were dilated. The right ventricle measured 11.5 cm. cephalocaudad and up to 10 cm. laterally; the left ventricle measured 10 cm. cephalocaudad. The tricuspid and pulmonary valves were natural; the pulmonary artery measured 8.5 cm. in circumference and showed slight atherosclerosis. The right ventricle showed moderate to marked hypertrophy and flattening of the endocardial surface. The left ventricle showed moderate to marked hypertrophy and dilatation. There were flattening and opacification of the endocardium over the interventricular septum. The papillary muscles showed moderate hypertrophy and endocardial opacification; they measured up to 1.3 cm. in greatest diameter. The mitral valve was normal. The aortic valve was thin and delicate, and showed no fusion



Fig. 6. Heart and aorta in situ. Note close similarity of outline of the heart and aorta to the mediastinal shadow in figure 5.



Fig. 7. Descending aorta. Note "tree-bark" appearance in certain areas.

or separation of the commissures. The aorta generally showed marked atherosclerosis with calcification. In a few areas, however, which measured up to 5 cm. in greatest extent the intimal surface had a well marked "tree-bark" appearance (figure 7). Commencing at the free edge of the aortic valve was a fusiform aneurysm which measured 13 cm. in length and 20 cm. in greatest circumference (figure 8). The



Fig. 8. Interior of left ventricle, aortic valve and aorta. Note the aneurysmal dilatation commencing just above the free edges of the aortic cusps. (Figure 7 is the close-up of the upper part of this photograph.)

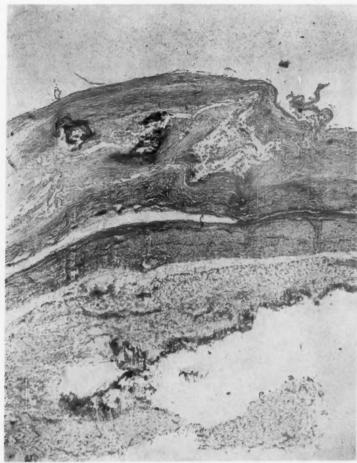


Fig. 9. Aorta. Note, in addition to atherosclerosis, lymphocytes scattered throughout the wall (×50).

wall of the aneurysmal sac varied from 0.2 to 0.7 cm. in thickness, and no thrombus was present.

The lungs were heavy (670 and 480 gm.) and showed numerous recent subpleural infarcts measuring up to 3 cm. The infarcts were associated with arterial thrombosis (? emboli). The liver and spleen showed passive congestion. The remaining organs were normal except for a completely bifid ureter on the right.

Histologically, much of the intima of the aorta showed atheromatous change, with acellular eosinophilic material, calcification, cholesterol clefts and a sprinkling of lymphocytes, foam cells and pigment-laden macrophages. The media showed mild to moderate variation in thickness. Some areas revealed only mildly distorted patterns, in which there were occasional lymphocytes and slightly increased numbers of capillary vessels. Elsewhere in the media, linear, undulating, colorless areas were

present, in some of which there were occasional slender acellular fibrils. In these areas the stromal cells were increased in number and more prominent than usual. They were usually elongated, mildly vesicular, and in instances were arranged in other than parallel directions. In other areas, moderate numbers of lymphocytes, a few probable fibroblasts and an uncommon neutrophil were present. Verhoeff's elastic stain showed moderate disruption of the elastic fibers in much of the media, and patches in which elastic tissue was absent. In the adventitia there were small numbers of lymphocytes which were commonly perivascular. The vasa vasorum were not unusual (figures 9 and 10). Sections of the mitral, tricuspid, pulmonary and aortic valves were entirely normal. There were mild to moderate diffuse hypertrophy of the myocardial fibers and nuclei and a few tiny areas of interstitial, mildly hyaline,



Fig. 10. Aorta. Note prominent lymphocytic infiltrate.

relatively acellular fibrosis, which were commonly not perivascular in location. In a few areas the endocardium was thickened by acellular, dense, eosinophilic material.

No inflammatory changes were found.

The thyroid showed interstitial fibrosis and acinar atrophy. There was chronic passive congestion in the liver, spleen and lungs. In addition, areas of recent infarction and arterial thrombosis (? emboli) were present in the lungs. Sections of the remaining organs showed no abnormalities.

Review of the slides of the subcutaneous nodule removed in 1946 showed a

typical rheumatoid nodule.

DISCUSSION

Despite the absence of rheumatoid "granulomas" in the heart or aorta such as those described by others, 2, 3, 4, 9, 10 we feel there can be little doubt that this is an unusually severe case of rheumatoid aortitis. The histologic picture in our case strikingly resembles that described by Mallory in 1936. 13, 14 He presented two cases and stated that, although the microscopic findings were almost identical with those of syphilitic aortitis, in view of a negative history of syphilis and negative serologic examination in each case he did not believe that syphilis was present. These two cases have subsequently been accepted as rheumatoid aortitis by Clark and others, 12 who consider that they are the first reported cases of rheumatoid aortitis. These latter authors also stress the remarkable similarity of these changes to those occurring in syphilitic aortitis. 12

In our case, syphilitic infection can be ruled out by the negative history of venereal infection and by numerous negative serologic examinations, such as those performed at the time of marriage and of induction into the Army, as well as by private physicians and during the patient's numerous hospital admissions.

There are several unusual features in this case, notably the appearance of both clinical and x-ray evidence of aortitis after the joint changes had completely regressed. We believe that this is the first reported case where there was no evidence of active arthritis or spondylitis while aortitis was present. Our case also differs from most of those previously reported in that the entire aorta was affected, and that there was massive aneurysmal dilatation of the ascending aorta with dilatation of the aortic valve ring. This latter finding only was responsible for the aortic regurgitation, the aortic valve cusps themselves having been completely normal. In other reported cases of aortitis there has been moderate to marked distortion of the aortic valve, either alone or in combination with other valves, and the inflammatory changes extended only a short distance into the aorta from the base of the valve leaflets. 12, 9, 18, 14 The remainder of the aorta was normal 2, 3, 7, 10, 13, 14 except in Gruenwald's case, where there was an aneurysm of the abdominal aorta which he considered to be atherosclerotic in type. 4

SUMMARY

The clinical and pathologic findings in a case of rheumatoid aortitis with aortic regurgitation and aneurysmal dilatation of the aorta are presented. We believe that this is the first reported case where the aortitis and arthritis were not present simultaneously and where the heart valves were completely normal.

ACKNOWLEDGMENT

We wish to express our thanks to Dr. Paul Klemperer, Mount Sinai Hospital, New York, who kindly reviewed the slides and concurred with our diagnosis.

SUMMARIO IN INTERLINGUA

Es reportate le caso de un masculo san de racia blanc qui disveloppava un sol episodio de arthritis rheumatoide al etate de 33 annos, manifeste in polyarthritis associate con dolor, tumefaction, e rubor de multe articulationes, incluse illos del manos e cubitos. Nodulos subcutanee appareva e persisteva durante periodos de usque a plure menses. Le biopsia de un tal nodulo revelava que il se tractava del typic nodulo subcutanee de arthritis rheumatoide. Nulle murmures cardiac e nulle allargamento del corde esseva presente a iste tempore. Omne apparente signos de arthritis dispareva ante le etate de 36 annos quando un minimo de allargamento cardiac e de dilatation aortic esseva notate in un roentgeno-examine routinari. Iste phenomenos progredeva e al etate de 40 annos esseva associate con functional insufficientia aortic. Al etate de 42 annos, al tempore del ultime hospitalisation del patiente, sever grados de disfallimento cardiac esseva constatate insimul con un marcate allargamento del corde e del aorta thoracic proximal. Numerose determinationes serologic pro lues, commenciante ante le declaration de arthritis, esseva negative.

Le necropsia revelava hepatomegalia, ascites, e atrophia e fibrosis del glandula thyroide como phenomenos post-therapeutic (I¹³¹). Nulle signo de arthritis esseva presente. Le corde occupava plus que un tertio del cavia thoracic e habeva un peso de 650 g. Le valvulas esseva tenue e delicate. Histologicamente illos esseva normal. Ambe ventriculos monstrava hypertrophia e dilatation de grados moderate o marcate. Esseva etiam notate plure areas microscopic de fibrosis myocardial (communmente non perivascular) e de fibrosis endocardial. Le aorta exhibiva un aneurysmo fusiforme, commenciante al margine libere del valvula aortic e mesurante 13 cm in longor e 20 cm in circumferentia maximal. Le pariete habeva un spissitate de 0,2 a 0,7 cm e revelava nulle thrombose. Le superficie intimal revelava marcate grados de atherosclerosis, con calcification diffuse e plure areas del apparentia de "cortice de arbore." In le examine microscopic le aorta revelava grados moderate o marcate de atherosclerosis. Le tunica medie monstrava focalmente disruption o mesmo absentia de fibras elastic e alicun lymphocytos. Le adventitia revelava micre numeros de lymphocytos, usualmente perivascular. Le vasa vasorum non esseva inusual.

Isto es le prime reportate caso de progressive aortitis rheumatoide con progression continue post le complete e permanente remission del rheumatoide affection articular.

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RENAL FUNCTION DURING PREGNANCY COMPLICATED BY INTERCAPILLARY GLOMERULOSCLEROSIS: SERIAL STUDIES IN A YOUNG DIABETIC *

By ETHAN A. H. SIMS, M.D., F.A.C.P., Burlington, Vermont

INTRODUCTION

RECENT studies of renal function in normal pregnancy have indicated that the renal plasma flow and glomerular filtration rate are increased roughly 50 and 30% respectively, particularly during midpregnancy.^{1,2} It is known that diabetic patients may enter pregnancy with renal function impaired as a result of intercapillary glomerulosclerosis (Kimmelstiel-Wilson syndrome), but may nevertheless successfully complete pregnancy without further deterioration of renal function, although in general the presence of nephritis places the patient in a relatively poor prognostic category.3 However, little is known about the course of pregnancy with respect to renal function in these patients and how it compares with the normal. In the present study, serial measurements of renal clearance have been made in a young female diabetic with proved intercapillary glomerulosclerosis established by renal biopsy to determine whether the kidney is capable of responding to the trophic stimuli of pregnancy, or whether the impairment of renal function becomes relatively more marked as pregnancy progresses.

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METHODS

The analytic methods and technic for measurement of renal clearances by a constant infusion technic were identical to those employed in this laboratory for a study of kidney function in normal pregnancy.2 Glomerular filtration rate was estimated by means of inulin. In the determination of inulin by the method of Schreiner, correction was made for the interference of glucose in plasma and urine. It was found that 100 mg, per 100 ml, of glucose were equivalent as a chromagen to 1.5 mg. per 100 ml. of inulin.4 Inulin and para-aminohippurate (PAH) were added to priming and sustaining infusions of 5% dextrose in water. To minimize the conjugation with dextrose, which may result in lower apparent values for renal plasma flow,5 the para-aminohippurate was added only just before use. It has been shown by Bucht et al. that in diabetic nephropathy the extraction ratio for para-aminohippurate may be reduced, but since this was noted only in those cases with substantial reduction of filtration rate, the clearance of PAH in this study is taken to approximate renal plasma flow. Urinary protein was estimated by the method of Purdy.7 Smears and cultures of urine were made at the time of catheterization, at the start of each clearance study. The optic fundi of the patient were studied at intervals by two separate observers, and drawings were made of the lesions noted.

CASE REPORTS AND RESULTS

A 22 year old married schoolteacher was admitted to the Medical and Obstetric Services at the Mary Fletcher Hospital on October 17, 1956, for evaluation of proteinuria and hypertension, noted in the ninth week of her first pregnancy.

At the age of five, following a bout of scarlet fever, the patient was found to have glycosuria. This was well controlled during her pre-adolescent years by a regimen of a weighed diet, and mixed protamine zinc insulin up to 12 units with regular insulin up to 26 units. There had been one episode of acute urinary infection, without known sequelae, in her fifth year. Catamenia was normal at age 14. From ages 14 to 16 she rebelled against her strict regimen, did not follow her diet, and required slightly more insulin. At about age 16 she developed osteomyelitis of the femur, which was successfully treated with penicillin. At this time proteinuria was first detected, but it subsequently cleared. She resumed a careful regimen, and during her high school and college years avoided excessive glycosuria, but had mild insulin reactions—roughly, once a week. Several days prior to her admission, in her ninth week of pregnancy, she consulted her obstetrician, who found hypertension of 170/80 mm. of Hg and moderate proteinuria. There was no dysuria or nocturia prior to pregnancy. Her weight had been constant at 127 pounds since adolescence. Past history and family history were essentially noncontributory.

On physical examination the patient was found to be a well nourished, alert young woman of short stature, with sallow skin and slight edema of the face. Her blood pressure was 120–140/68–90 mm. of Hg; pulse rate, 96. Significant physical findings were as follows: Both fundi had small, hard white exudates and microaneurysms, mostly in the macular regions, and more numerous in the left fundus than in the right. In one quadrant on the left there were a few small flame-shaped hemorrhages. These findings were considered by a consulting ophthalmologist to be typical of early diabetic retinitis. Deep reflexes of the lower extremities were absent, but sensory modalities were intact. The dorsalis pedis pulsations were only faintly palpable bilaterally.

Initial laboratory findings included a hemoglobin of 12.8 gm., and a packed cell

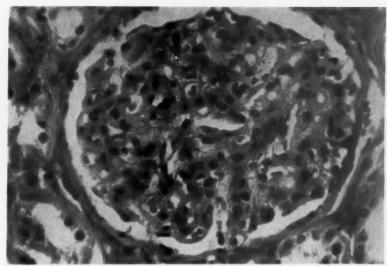


Fig. 1. Photomicrograph of a typical glomerulus, showing thickening of basement membrane. \times 400.

volume of 38%. Several urine samples had rare red blood cells and rare white blood cells per high power field, but no casts. Plasma urea nitrogen was 13 mg. per 100 ml. Serum albumin was 3.8 gm. %; serum cholesterol, 290 mg. per 100 ml. Proteinuria during 24 hours of recumbency was 0.52 gm. An x-ray of the chest

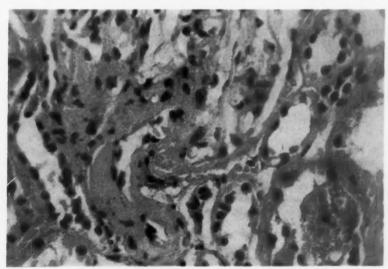


Fig. 2. Photomicrograph of afferent glomerular arteriole, showing intimal thickening. \times 400.

showed no abnormality, and there was no calcification of the blood vessels of the lower extremities. On October 23 the patient was re-admitted for open biopsy of the right kidney. Blood pressure during this admission ranged from 120 to 150 mm. systolic and from 70 to 90 mm. diastolic. The renal biopsy showed all glomeruli to have thickening of the basement membrane and, in few instances, early nodular changes (figure 1). A rare glomerulus was completely hyalinized. Many of the arterioles showed severe thickening of the wall with amorphous hyaline material, and associated with this change there was corresponding severe luminal narrowing (figure 2). In spite of these changes, the glomeruli in general appeared to be well vascularized. Initial renal function studies were as follows: inulin clearance 103 ml. per minute (corrected to a standard surface area of 1.73 sq. M.); clearance of PAH was 895 ml. per minute, giving a reduced filtration fraction of 0.11.

TABLE 1 Clinical Findings

| Time (Weeks) | Blood Pressure (mm, Hg) | Weight (lbs.) | Plasma Urea Nitrogen (mg./100 ml.) | Proteinuria (gm./24 hours |
|-----------------|----------------------------|------------------|--|------------------------------|
| Ante-partum 10 | 120-150 70-80 | 130 | 13 | 0.52 |
| 16 | 120-130 70-80 | 130 | 19 | - |
| 20 | $\frac{138-146}{78-82}$ | 133 | 18 | 2.8 |
| 24 | $\frac{122-140}{70-80}$ | 133 | 15 | 0.6 |
| 30 | 138 80 | 137 | 18 | 1.6 |
| 35 Post-partum | 140-160 88-100 | 139 | 19 | 2.4 2.8 |
| 1 | $\frac{130}{70}$ | 113 | 16 | + |
| 10 | 110 70 | 130 | 20 | + |

COURSE OF PREGNANCY AND SERIAL FUNCTION STUDIES

Clinical findings are outlined in table 1.

Blood Pressure: During the midtrimester the blood pressure continued to range from 120 to 145 mm. systolic and from 70 to 82 mm. diastolic. In the third trimester, systolic pressures gradually rose from 135 to 160 mm. and diastolic from 80 to 90 mm. Venous pressures, measured at the end of the infusions in the clearance studies, remained normal.

Retinal Changes: As pregnancy advanced, what hemorrhagic lesions were originally present became pale and apparently fibrosed, and the capillary aneurysms decreased in prominence. No hemorrhagic or aneurysmal lesions developed until a few days prior to cesarean section.

Proteinuria per 24 hours, measured while the patient was ambulatory, was 2.8 gm.

at 20 weeks, 0.6 gm. at 24 weeks, 1.6 gm. at 30 weeks and 2.4 and 2.6 gm. just prior to cesarean section.

Control of Diabetes: Control of diabetes was satisfactory, with mixed protamine zinc insulin increasing from 8 to 16 units at term with regular insulin increasing from 20 to 34 units at term. Glycosuria was moderately well controlled, and ketonuria was negligible.

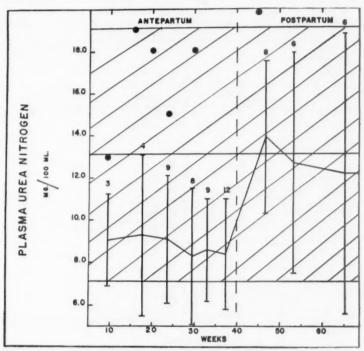


Fig. 3. The concentration of urea nitrogen during pregnancy (solid circles) shown in relation to the normal range for nonpregnant subjects (shaded area) and the normal range for pregnant subjects. The mean is indicated by the solid line, and the bars indicate 2 S. D. above and below.

Urea Nitrogen: As shown in table 1, the patient's plasma urea nitrogen ranged between 15 and 19 during the great part of pregnancy. These values are abnormally high in relation to the normal range for this state of pregnancy of $8.5 \pm S$. D. 1.5 ml./100 ml., as shown in figure 3.

Delivery: On April 15, 1957, the patient was re-admitted in her thirty-fifth week of pregnancy. She had gained a total of 11 pounds during the pregnancy, and had no gross edema. Blood pressure was labile, with a maximum of 140/100 mm. of Hg. There was borderline polyhydramnios. One relatively fresh small hemorrhage was noted in the optic fundus. On April 19 the patient was delivered by cesarean section of a moderately edematous male infant weighing 3,750 gm.

Renal Function Studies during Pregnancy: The patient's findings in relation to the normal range throughout pregnancy are shown in figure 4. When first studied,

this patient had a renal plasma flow significantly higher than the normal for non-pregnant subjects. In association with this, the inulin clearance, while within the usual normal range, was significantly low for the tenth week of pregnancy, resulting in low filtration fraction. There was a further rise in plasma flow to 1,000 ml. per minute by the sixteenth week, and to 900 ml. per minute by the twenty-fourth week, both of these values being at the extreme upper range of normal for this stage of pregnancy. Thereafter there was a decline to 790 ml. per minute by the thirtieth week, six weeks prior to delivery by cesarean section. The clearances of inulin rose to a maximum of 150 ml. per minute by the twenty-fourth week, bringing the filtration

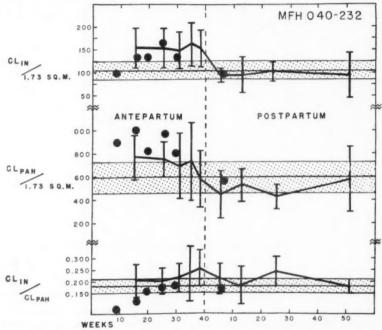


Fig. 4. Diagram showing values of serial renal function studies during pregnancy in a patient with glomerulosclerosis. The stippled areas represent the normal nonpregnant means and two standard deviations above and below. The heavy line represents the mean of normal pregnant subjects; the bars, two standard deviations above and below the mean. The solid circles indicate values for the patient.

fraction to within the normal range. By the thirtieth week the clearance of inulin was still increased to 133 ml. per minute, and the filtration fraction remained normal. Just prior to section an endogenous creatinine clearance was 109 ml. per minute. The normal range for this stage of pregnancy is 145 ± 22 ml./minute.

The patient was kept glycosuric during each clearance study with blood sugars of from 250 to 350 mg./100 ml., so that tubular reabsorption of glucose could be measured. The ratio of filtered to reabsorbed glucose was 1.6 in the first study, and from 1.1 to 1.3 in all subsequent studies, so that maximal reabsorption (Tmo) was not measured. Tubular reabsorption was higher (360 and 324 mg./minute) in the last half of pregnancy than in the first (281, 322 and 288), and also higher than in the puerperium (273 mg./minute).

Postpartum Studies: At 10 weeks postpartum the clearance of inulin was close to the mean for normal nonpregnant subjects. The plasma flow was relatively high in relation to subjects in the puerperium, but well within normal range. The filtration fraction remained within the normal range, and was 70% higher than early in the pregnancy. At this time the patient's blood pressure was 110/70 mm. of Hg and the hematocrit was 36%.

DISCUSSION

Certain features of this case suggest that, in response to the stimuli of pregnancy, there was an actual improvement in the disease of small blood vessels.

Regression of the lesions of the optic fundi was noted until shortly before delivery. This is at variance with the findings in pregnant diabetics with neuropathy summarized by Becker,⁸ but consistent with those of Ditzel and Moinat,⁹ who noted no gross progression of retinopathy in their series of 30 pregnant diabetic patients. They did, however, note progressive changes in the conjunctival blood vessels in normal pregnancy, and more marked changes in

pregnancy in diabetic subjects.

This patient initially presented a low filtration fraction consistent with the universal involvement of the basement membranes of the glomeruli seen on the renal biopsy. All of the 10 young patients with diabetic nephropathy studied by Bucht et al.⁶ had reduced filtration fractions. However, in the series of 12 patients with various stages of intercapillary glomerulosclerosis studied by Brun, ¹⁰ only one, who was found on renal biopsy to have predominantly diffuse lesions, had a reduced filtration fraction. As pregnancy advanced, however, renal clearance of inulin and of PAH reached values which were elevated in relation to those of normal nonpregnant women, and also in relation to the patient's own postpartum studies. However, an elevated filtration rate per se does not necessarily point to the integrity of the glomerular capillary loops, since, in certain cases of the nephrotic syndrome with heavy proteinuria, high filtration rates may be seen. ¹¹ Unfortunately, it was not possible to obtain a second renal biopsy to determine whether anatomic improvement accompanied the increase in renal blood flow and filtration rate.

The finding in this patient of concentrations of plasma urea nitrogen well above the normal range for pregnancy is paradoxical in the face of elevated glomerular filtration rates. A relatively high intake of protein and high rate of catabolism of tissue protein secondary to glycosuria may each have contributed in some degree. Another possible explanation may lie in the fact that kidney function studies, as conventionally carried out with the patient reclining, particularly in pregnancy may not be representative of the function during ambulation. It has been shown by Diagnam et al.¹² that, on quiet standing, the pregnant patient has a marked fall in filtration rate and excretion of sodium as a result of venous pooling and redistribution of body fluids. The high filtration rate of pregnancy might be regarded as compensatory for these postural changes. The possibility cannot be ruled out in the present case that while the patient was normally erect or ambulatory during a large portion of the day, the filtration rate was in fact reduced to a point which would explain the relatively high values of blood urea nitrogen.

During the course of pregnancy in this subject there was no rise in tubular reabsorption of glucose adequate to compensate for the increase in filtration

rate. It is thus evident that, during pregnancy, glycosuria must have developed at correspondingly lower serum concentrations than prior to pregnancy. In a study of 110 pregnant diabetic women, Mohnike and Worm observed excretion of glucose at progressively lower blood levels up to the thirty-fourth week of pregnancy.¹⁸ It has been shown in this laboratory that a similar mechanism may explain the development of glycosuria with normoglycemia in certain normal pregnant patients.¹⁴

A number of mechanisms might be responsible for the changes in renal function observed. It has been suggested that an elevation of the concentration of glycoproteins may lead to the formation of capillary lesions in diabetes from their deposition in renal and retinal vessels.^{15, 16} A decrease in their concentration in pregnancy might thus have a favorable effect. However, high concentrations of glycoproteins may be unassociated with such capillary lesions,¹⁷ and no important changes in the concentration of glycoproteins during the course of normal

pregnancy or pregnancy in the diabetic have been noted.9

It is perhaps more reasonable to assume that the factors producing the changes in renal function noted in this case are the same as those which produce augmented renal function in normal pregnancy. There is considerable indirect evidence that this is the result of increased secretion of endocrines in pregnancy, notably of pituitary somatotropin, of adrenal cortical steriods, and possibly of thyroid hormone. The evidence for this has been reviewed in detail in a recent publication.² It seems unlikely, however, that the increased secretion of adrenal corticoids should be the predominant factor, since there is some evidence that adrenal cortical hyperactivity may in fact facilitate or aggravate the lesions of small blood vessels in diabetes.⁸ There is also the fact that hypophysectomy may ameliorate vascular and renal lesions ¹⁸ in patients with the Kimmelstiel-Wilson syndrome.

No definitive conclusions can be drawn from the present single and limited study, other than that extensive involvement with the diffuse form of intercapillary glomerulosclerosis does not prevent the development of supernormal renal function in pregnancy. Further serial studies with serial biopsies are required to determine whether other patients with varying stages of glomerulosclerosis may show similar changes.

SUMMARY

Serial renal function studies have been carried out during pregnancy in a 22 year old woman with juvenile diabetes of 18 year's duration. At the onset of pregnancy there were labile hypertension, moderate proteinuria, mild retinopathy, and diffuse intercapillary glomerulosclerosis on renal biopsy. The clinical course was favorable, and the retinopathy improved until just prior to delivery.

During pregnancy there was increase of renal function similar to that seen in normal pregnant subjects. The glomerular filtration rate and estimated renal plasma flow rose to roughly 50% above the normal mean for nonpregnant subjects, and the filtration fraction, initially abnormally low, became normal and remained so during the postpartum period.

Tubular reabsorption of glucose was not increased concomitantly with the

increase in filtration, so that glycosuria was possible in the face of lower concentrations of glucose in the plasma.

Possible mechanisms for the increase in renal function are discussed.

ADDENDUM

Since preparation of this manuscript evidence has accumulated in our laboratory that when PAH is added to infusions of glucose in the course of clearance studies according to the method described above, it does not undergo significant Shiff base conjugation with glucose in vitro or in vivo, but that on standing at room temperature conjugation may occur in the urine of patients with glucosuria, so that the apparent content of free PAH is reduced. The urines in this study were analyzed for PAH with minimal delay or were frozen soon after collection. Any error from partial conjugation of PAH with glucose would minimize the actual elevation of effective renal plasma flow noted in these studies.

ACKNOWLEDGMENTS

The author is indebted to Dr. John Van S. Maeck, attending obstetrician and Chairman of the Department of Obstetrics, for referring this patient and for his suggestions and cooperation throughout these studies.

We wish to express our appreciation to Mrs. Margaret Tjaden for able technical

assistance.

SUMMARIO IN INTERLINGUA

Recente studios serial del function renal in normal pregnantias ha indicate que le fluxo de plasma renal e le intensitate del filtration glomerular es augmentate per circa 50 e 30 pro cento, respectivemente. Il es cognoscite que patientes diabetic con moderatemente avantiate grados de glomerulosclerosis intercapillar pote completar un pregnantia a bon successo e sin apparente deterioration del function renal. Tamen, pauco es cognoscite relative al alterationes del function renal que occurre in tal patientes in le curso del pregnantia.

Sex studios serial esseva effectuate inter le comenciamento del decime e le fin del trentesime septimana del pregnantia e post parto in un juvene femina de 22 annos de etate con un historia de diabete de 18 annos de duration. In le none septimana, hypertension de 170/80 mm de Hg esseva constatate; etiam leve grados de retinopathia diabetic sed nulle calcification arterial secundo le roentgenogramma. Un aperte biopsia renal monstrava leve a moderate grados de spissification uniforme del membrana basilar del ansas glomerular insimul con spissification intimal de multe

arteriolas e un pauco frequente hyalinisation de glomerulos individual.

Le mesura del filtration glomerular al decime septimana del pregnantia esseva 103 ml per minuta. Le fluxo de plasma renal esseva 895 ml per minuta, de maniera que le fraction de filtration amontava al basse valor de 0,11. Le areas del valores normal a iste stadio del pregnantia, secundo le experientias de nostre laboratorio, es 155 ± 22 ml per minuta pro le mesura del filtration glomerular; 770 ± 93 ml per minuta pro le fluxo de plasma renal; e 0,21 \pm 0,035 pro le fraction de filtration. Sex septimanas plus tarde, in le dece-sexte septimana del pregnantia, le mesura del filtration glomerular habeva montate a 130 ml per minuta, e le fluxo de plasma renal esseva 1.030 ml per minuta. In le vinti-quarte septimana le mesura del filtration glomerular esseva 153 ml per minuta e le fluxo de plasma renal esseva 963 ml per minuta, i.e., le fraction de filtration—amontante a 0,16—habeva montate sed esseva ancora infra le norma. Le valores normal a iste stadio es 152 ± 22 ml per minuta pro le mesura del filtration glomerular, 759 ± 77 ml per minuta pro le

fluxo de plasma renal, e 0.20 ± 0.027 pro le fraction de filtration. Post 30 septimanas de pregnantia, le mesura del filtration glomerular e le fluxo de plasma renal descendeva a 133 e 794 ml per minuta, respectivemente, i.e., le fraction de filtration habeva montate additionalmente a 0.17. Sex septimanas post parto le mesura del filtration glomerular esseva 99 ml per minuta. Le fluxo de plasma renal esseva 589 ml per minuta. Le fraction de filtration habeva assi perseverate al nivello de 0.17. Mesurationes serial del re-absorption tubular de glucosa non revelava variationes significative. Al medio del pregnantia le proteinuria se clarificava. Il occurreva regeneration e cicatrisation del active lesiones retinal, e iste phenomeno persisteva usque al nascentia del infante qui esseva normal.

Super le base de iste studio, il pare que un ren con grados moderate de glomerulosclerosis intercapillar pote nonobstante responder al stimulos trophic de un pregnantia normal per disveloppar un function supranormal e que le augmento del fraction de filtration pote perseverar durante un certe periodo post parto.

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FATAL METHEMOGLOBINEMIA DUE TO WELL WATER NITRATES*

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Among the many causes of acquired methemoglobinemia, that due to ingestion of well water containing high levels of nitrates is an entity one should consider in a cyanotic infant with a negative history and physical findings. Some other causes of methemoglobinemia are aniline, phenacetin, acetanilid, sulfonamides, nitrobenzene, various nitrites, nitroglycerin, bismuth subnitrate, ammonium nitrates, contact with dyed blankets, laundry marks on diapers, freshly dyed shoes, inhalation of nitrous gases in arc welding, and ingestion of cravons containing p-nitroaniline.⁵

Methemoglobin is a derivative of hemoglobin, where ferrous porphyrin complex is converted to the ferric form, which does not combine with oxygen.³ It can be reduced to hemoglobin by reducing agents such as methylene blue, ascorbic acid or glutathione. The normal concentration of methemoglobin in the blood is 1.7% or less, because in the intact erythrocyte, methemoglobin is continuously formed and reduced.⁴ Various chemical compounds which convert hemoglobin to methemoglobin preferentially oxidize hemoglobin, and reducing substances in the body offer no protection against oxidation. Thus the tissues are liable to anoxemia not only from loss of oxygen capacity of the blood but also from increasing difficulty in unloading from the blood such oxygen as is available.⁵

The characteristic picture of cyanosis begins around the lips and spreads to the fingers, toes, face and eventually over the entire body. This is usually aggravated by crying. A blood sample is typically chocolate brown in color. Heinz bodies, though not specific for this disease, may be seen in wet, unstained preparations as refractile, irregularly shaped bodies, often lying at or close to the periphery of the erythrocyte, or sometimes attached to the outer surface of the wall.⁵

In treatment methylene blue is more useful than ascorbic acid, as it brings about reversion of methemoglobin by acceleration of the normal mechanism, rather than by a process which is slower than the normal cell conversion system. One milligram per kilogram of body weight of methylene blue in a 1% solution injected intravenously over a period of five minutes is the recommended dose in adults. In infants, 2 mg. per kilogram of body weight should be administered in a similar manner. If the cyanosis has not disappeared in one hour, an equal dose is repeated. Where there is no urgency, methylene blue may be given orally in doses of 3 to 5 mg. per kilogram of body weight. If well water nitrates is the cause, there is spontaneous disappearance of the cyanosis within 48 hours after changing the water used in the feeding formula.

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It is necessary for the nitrates in the well to be present in at least 10 to 20 parts per million before cyanosis develops.

In the intestinal tract, ingested nitrates may be reduced to nitrites by bacterial action. As a result of their experiments, Cornblath and Hartman postulate that, in infants with no free acid in the stomach and the pH of the gastric juice over 4.0, nitrite-producing organisms can exist high in the gastrointestinal tract in sufficient numbers to reduce nitrates to nitrites before the former can be completely absorbed. In older infants with increased gastric acidity, the growth of the nitrite-reducing bacteria is inhibited.² Thus, after the second month they are less likely to develop this poisoning.

CASE REPORT

A 20 day old Mexican male was brought to the emergency room of this hospital in a semiconscious state at 7:50 a.m. The father did not speak English, and it was only after a delay that a reasonable history was obtained posthumously through an interpreter. The infant was the product of a full term, uncomplicated pregnancy and low forceps delivery. The birth weight was 2,386 gm. At 6.00 a.m. on the day of admission he had begun to scream and then turned blue. On examination he appeared to be undernourished and of small stature. The respirations were markedly decreased, and he had a mottled color all over his skin. There was no movement of the extremities. The lungs had good exchange, with a few crepitant râles. The apical heart rate was 70 per minute. Artificial respiration brought forth milk and mucus secretions, so the nasopharynx was aspirated. Positive pressure oxygen, caffeine and mouth-to-mouth respiration were administered, to no avail, and the child died a few minutes later. The possibility of aspiration pneumonia or congenital heart disease was entertained in the emergency room.

At autopsy the body was that of a poorly nourished, well developed white male infant, weighing 2,460 gm. The most striking finding was the presence of dark brown blood in the cardiac chambers and major blood vessels, which suggested methemoglobinemia. The brain, lungs, liver, kidneys, spleen, adrenals, pancreas, heart and major blood vessels showed no abnormalities. Studies on the blood drawn at the start of the autopsy showed a hemoglobin of 8.7 gm.%, with 74% methemoglobin (6.43 gm.%).

The health authorities were alerted, and an analysis of the well water used by the family showed the nitrate content to be 580 parts per million. The well was 16 feet deep, and the water in a neighboring well 200 feet away was "normal." Further questioning of the infant's aunt revealed that he had been having cyanotic spells for the last three days, more marked during crying.

SUMMARY

A fatal case of methemoglobinemia due to ingestion of well water containing a high nitrate concentration is reported. Treatment and pathogenesis are briefly discussed. It is suggested that, particularly in rural areas, this entity be considered in a young infant with cyanosis and a negative history and physical findings.

SUMMARIO IN INTERLINGUA

In casos de methemoglobinemia, le ingestion de aqua de puteo continente alte concentrationes de nitrato debe esser prendite in consideration como possibile factor

etiologic si le patiente es un infante con un historia negative e con negative constatationes physic. Methemoglobina es un derivato de hemoglobina. In illo le originalmente ferrose complexo de porphyrina es convertite in le forma ferric que non es capace de combinar se con oxygeno. Typicamente, le resultante cyanosis comencia in le labios e se extende al digitos del manos e pedes, al facie, e al corpore integre. Un specimen de sanguine exhibi un coloration brun chocolate. Le nitratos in le aqua de puteo debe esser presente in un concentration de al minus 10 a 20 partes per million ante que cyanosis pote disveloppar se. Le tractamento con blau methylenic es plus efficace que le uso de acido ascorbic o glutathiona. In infantes, 2 mg per kg de peso corporee de un solution de 1% de blau methylenic es administrate intravenosemente in le curso de un periodo de cinque minutas. Si le cyanosis non ha disparite al fin de un hora, le administration del mesme dose es repetite. In adultos, 1 mg per kg de peso corporee es administrate intravenosemente. Si le situation es sin urgentia 3 a 5 mg per kg pote esser administrate per via oral.

Recentemente, un infante mascule mexican de 20 dies de etate esseva presentate al sala de urgentia in stato de semiconscietate e moriva alicun minutas plus tarde. Al domicilio de su parentes ille habeva comenciate critar e postea devenir blau. Post su arrivata al hospital, il esseva constatate que su respirationes esseva marcatemente reducite. Su color esseva generalmente maculate. Le excambio pulmonar esseva bon. Le frequentia cardiac apical esseva 70 per minuta. Respiration artificial, oxygeno sub pression positive, e caffeina per via intramuscular remaneva sin effecto. Le necropsia constatava micre statura con subalimentation e un peso de 2460 g. Le plus frappante observation necroptic esseva le presentia de sanguine de color brunobscur in le corde e le major vasos sanguinee. Isto suggereva methemoglobinemia, Le cerebro, le pulmones, le corde, le vasos de sanguine, le hepate, le splen, le pancreas, le corpores suprarenal, e le renes esseva microscopicamente normal. Le studio de un specimen de sanguine obtenite al comenciamento del necropsia revelava un contento de hemoglobina de 8,7 g%, con 6,43 g% de methemoglobina. Le analyse del aqua de puteo usate per le familia revelava un contento de nitratos amontante a 580 partes per million. Un interrogatorio additional revelava que le infante habeva habite episodios de cyanosis durante le passate tres dies. Istos habeva essite le plus marcate

Cornblath e Hartman ha postulate que in infantes con nulle acido libere in le stomacho e un pH del succo gastric de plus que 4,0, il es possibile pro organismos nitrito-productori de exister in alto in le vias gastrointestinal in numeros sufficiente pro reducer nitratos a nitritos ante que le nitratos es completemente absorbite. In infantes de etate plus avantiate, con augmento del aciditate gastric, le crescentia de iste organismos es inhibite. Assi, post le secunde mense del etate, le infante curre un minus forte risco de contraher iste morbo.

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DERMATITIS. HEPATITIS AND NEPHRITIS DUE TO PHENINDIONE (PHENYLINDANDIONE) *

By R. H. Brooks, M.D., and H. B. CALLEJA, M.D., Columbus, Ohio

THE last decade has seen universal acceptance of anticoagulant therapy in thromboembolic diseases. In the treatment of individual cases, however, particularly those of acute coronary occlusion, opinion varies as to which cases should receive anticoagulants, and how long therapy should be continued. In addition, hemorrhage is generally accepted as a calculated risk directly attributable to the very nature of the therapy, regardless of the type and kind of anticoagulant used. Indeed, fatal hemorrhagic complications have occurred. Cautious, close supervision of the patient, better knowledge of the type of drug used, and due respect for established contraindications must be emphasized if a fatal hemorrhagic episode is to be avoided.

It is agreed that toxicity should be low or even absent for an anticoagulant to meet one of the criteria of an "ideal" oral anticoagulant. Early clinical reports on the use of phenindione as an anticoagulant showed promising advantages over Dicumarol. However, in 1954, two reports of severe drug sensitivity reaction to phenindione appeared.^{1, 2} Both cases had fever, rash, blood abnormalities and jaundice.

Review of the world literature to date shows four cases of severe reaction, consisting of the symptom-complex of fever, rash, blood dyscrasia and jaundice due to phenindione (table 1). We are reporting another case who developed the above symptomatology, including nephritis, as manifestations of a severe drug reaction following phenindione therapy.

CASE REPORT

A 41 year old Negro male was admitted to the Ohio Penitentiary Hospital on June 4, 1958, within one hour of the onset of an acute coronary attack. Serial electrocardiograms showed an acute anterior myocardial infarction. The only history pertinent to this report is that of a mild hay fever for the last few years which did not require treatment. The patient gave no history of liver or kidney disease. His physical examination was not remarkable. On admission his urinalysis and complete blood count were normal, and when repeated on June 26 were again normal. The patient was placed on routine coronary care, and Hedulin (phenindione) was started the day following admission. An average dose of 90 mg. per day of Hedulin was enough to keep his prothrombin time within therapeutic levels.

The patient's progress was satisfactory until June 21, 1958, when he became febrile. Eight days later he developed a generalized morbilliform eruption, and Nembutal was discontinued immediately. The fever, however, continued, with an average temperature of 102° F., and the rash became intensely pruritic and exfoliative.

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TABLE 1 Severe Reactions to Phenindione

| Author | Age and Sex | Fever | Rash | Blood Abnormalities | Liver Tests | Dose | Remarks |
|---|----------------|----------------------|---|---|--|--|--|
| . Makous and Vander Veer June, 1954 | 42 F | 101.6°- 104.6° F. | Morbilliform | Leukemoid reaction, young forms, eosino- philia, anemia: platelets low. | Obstructive and hepatocellular damage; liver palpable and tender. | 266 mg./day. Discontinued 10 days after onset of reaction. | Onset, 15th day, Albuminuria, 2+ B, proteus in urine culture. |
| 2. Kirkeby Sept. 1954 | N N | 101.2°- 103.2° F. | Morbilliform | Leukopenia with agran- ulocytosis. Bone mar- row: hypoplasia of granulocyte elements and lack of myeloid maturation. | Jaundice—type? No evidence of hepatocellular damage. | 112.5 mg./day. Discontinued wk. after onset of reaction. | Onset, 28th day. Proteinuria for 3 days. Died of "lower neph- ron nephrosis." |
| 3. East and Beamish Dec. 1957 | 94 M | 102.5° F. | 102.5° F. Scarlatiniform | Neutropenia, young forms, atypical monocytes. | Obstructive and hepatocellular damage; liver palpable and nontender. | 223 mg./day. Discontinued 3 days after onset of reaction. | Onset, 15th day. |
| 4. Burns and Desmond June, 1958 | 59 M | 101.2°- 104° F. | Scarlatiniform and morbilli- form | Leukopenia with agran- ulocytosis, eosinophilia, atypical monocytes. Bone marrow: marked increase in eosinophils, (autopsy). | Obstructive. No hepatocellular damage | 125 mg./day. Discontinued 1 day after onset of reaction. | Onset, 27th day. Albuminuria, trace; granular casts, occ. |
| 5. Present report | 14 N | 102° F. | Morbilliform | Leukemoid reaction, eosinophilia; platelets low. | Liver palpable and tender. | 90 mg./day. Discontinued 10 days after onset of reaction. | Onset, 18th day, Albuminuria, granular casts, red blood cells, white blood cells in the urine. |

On July 1, 1958, Hedulin was discontinued. Jaundice was first noticed four days later. This was accompanied by epigastric bloating, loss of appetite, acholic stools, and a tender liver palpable two fingerbreadths below the right costal margin. His

icterus index reached its highest (44 units) on July 11, 1958.

On July 10, 1958, urinalysis showed 4 plus albuminuria, and three to five granular casts, six to eight red blood cells and five to seven white blood cells per high power field. The specific gravity was normal. Blood urea nitrogen was 10 mg.%. Complete blood count showed: white blood cells, 24,000, with 50% neutrophils, 11% cosinophils, 38% lymphocytes and 1% monocytes. Platelet count was 64,000; repeat count on July 1 showed 104,000. The hemoglobin and hematorit values were normal. Three subsequent urinalyses showed progressive disappearance of albuminuria and cellular elements; a fourth urine check (July 24, 1958) was completely negative.

ACTH, 40 units daily, was given from July 11 through August 7, 1958. On the latter date the patient was essentially asymptomatic, with no rash or jaundice, and his liver was no longer palpable. He was released on August 26, 1958, improved

from his acute coronary attack and free from his drug reaction.

On October 4, 1958, the patient was readmitted for a provocative test. He was given 50 mg. of Hedulin daily for two days. On the third day he developed the same generalized morbilliform rash as on June 26, 1958, but with no icterus or fever. After 10 days of treatment with Neo-antergan, 50 mg. every six hours, and Meticorten, 30 mg. for two days and then 5 mg. daily, the patient was again asymptomatic. However, for the 10 months following the provocative test he continued to have short episodes of pruritic morbilliform rash, controlled by resuming the above treatment for a few days. The only other medication administered while he was in the hospital was Nembutal. This he had taken before his acute coronary occlusion and after he was released from the hospital, with no apparent reaction.

Discussion

The clinical use of phenindione as an anticoagulant was introduced by Soulier and Gueguen³ in 1947. The toxic effects noted were dryness of the mouth, polydipsia, polyuria, tachycardia and renal damage. These authors originally

used larger doses than are currently used.

Burns and Desmond reviewed the literature on sensitivity to Dindevan (phenindione) and found seven cases of "serious drug sensitivity." Of these, two had fever, rash, blood dyscrasia and jaundice; two had fever, rash and blood dyscrasia; and three had only fever and blood dyscrasia. The case of East and Beamish and the patient reported by Johman were not included in their review. There was no autheticated case of fatality directly due to phenindione reaction. In Kirkeby's fatal case, the clinical diagnosis of "lower nephron nephrosis, possibly attributable to his allergic state," is questionable. Sensitivity reaction to phenindione could have been contributory to the death of the second patient in the series reported by Brown and MacMillan. However, neither of these fatal cases had an autopsy report.

From the cases so far reported it would seem that the onset and severity of the reaction are directly related to the dose of the drug used. The case of Makous and Vander Veer and the case of East and Beamish each received more than 200 mg. per day, and the drug was continued for 10 and 13 days, respectively, after the onset of the reaction. Both cases developed sensitivity reaction 15 days after phenindione was started. Likewise, both had evidences of parenchymal liver damage. The case of Burns and Desmond showed an obstructive

type of jaundice, without evidence of parenchymal liver damage. From the data available, the exact etiology of the jaundice in Kirkeby's patient is not entirely clear. Although no extensive liver function tests were done, from clinical evidence alone we think that hepatitis was present in our case. A tender and palpable liver, together with jaundice, was present only during the sensitivity reaction.

Nephritis has not to our knowledge been described as part of a severe reaction to phenindione, although Soulier and Gueguen noted decreased specific gravity of the urine and hematuria as evidence of renal damage. They believed this to be due to deposition of drug crystals in the tubules. It is, however, a difficult problem to evaluate hematuria as indicating renal damage in a patient under anticoagulant therapy. Coon et al.⁸ did careful serial urinalyses in 200 patients receiving phenindione, and found transient proteinuria (from a trace to 1 plus) in two thirds of their series. Proteinuria usually occurred within the first days of therapy, and disappeared in from one to four days, even if the drug was continued. Our case developed urinary abnormalities at the time of the sensitivity reaction. The chronology of events does not coincide with the transient and mild proteinuria expected from this treatment, and the greater degree of proteinuria with casts, plus the fact that repeated urinalyses before and after the sensitivity reaction were consistently negative, seems to support the premise that toxic nephritis was part of the sensitivity reaction in this patient.

The onset of skin rash is a valuable clue to a suspicion of sensitivity reaction in a patient receiving phenindione therapy. The futility of a serial leukocyte count has been emphasized by Burns and Desmond, since the blood abnormalities tend to come late. It is our belief that the drug should be discontinued whenever a skin rash appears, especially when accompanied by fever. While it is true that rash may develop with Dicumarol therapy and that the drug can be continued with no further reactions, in the case of phenindione, interruption of therapy with this drug is mandatory. It is fortunate that one may switch to another anticoagulant without developing another sensitivity reaction.

SUMMARY

1. A case is reported of severe drug reaction with dermatitis, hepatitis and nephritis due to phenindione. The world literature is reviewed.

2. The appearance of skin rash, with or without fever, in a patient receiving phenindione should draw attention to a sensitivity reaction to this drug. Immediate interruption of phenindione therapy is advocated.

SUMMARIO IN INTERLINGUA

Es reportate un caso de reaction sever a phenindiona (phenylindanediona) in un masculo negre de 41 annos de etate con acute occlusion coronari. Le reaction consisteva de febre, eczema, jalnessa, hyperesthesia del hepate que esseva palpabile, dyscrasia del sanguine, e anormalitates urinari que indicava injurias renal. Resultatos positive de un test de provocation con 50 mg de Hedulina per die durante duo dies confirmava le diagnose. Le therapia e phenindiona esseva discontinuate, e un rapide defervescentia del manifestationes del pharmacoreaction sequeva le institution del tractamento a ACTH. Es suggerite que le apparition de un eczema cutanee, con o sin febre, in un patiente sub therapia a phenindiona deberea facer pensar al pos-

sibilitate de un reaction de sensibilitate a iste droga. Le interruption immediate del therapia a phenindiona in tal casos es recommendate. Es revistate le pertinente litteratura mundial.

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EBSTEIN'S ANOMALY IN THE ADULT*

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A congenital anomaly consisting of downward displacement of the tricuspid valve in the right ventricle in a young man was described by Ebstein in 1866.1 Several articles with collections of such cases 2-5 have appeared recently, and occasionally this diagnosis has been made during life.6-7 Although there are reports of survivors to the seventh or eighth decade,8-10 for the most part compilations of cases have emphasized the occurrence of Ebstein's anomaly in infancy. Unfortunately, congenital heart disease is sought enthusiastically in the young, but is forgotten frequently in the older patient. As Ebstein's anomaly may be compatible with a long, active life, it is important that the clinical syndrome be appreciated in the adult.

CASE REPORT

Our patient, a 60 year old male at the time of his death, was seen at Saint Luke's Hospital intermittently between 1936 and 1957. In 1935, at the age of 38, he fell while at work and struck his head. He did not lose consciousness, and continued with his work as a machinist. Several mornings later he awakened with paresis of his left side. He was admitted to a hospital and sometime thereafter told that he

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had a "clot on his brain" and discharged. Between 1937 and 1957 he had four admissions to Saint Luke's Hospital because of convulsions and loss of consciousness. These episodes were distinctive, always beginning on arising from sleep. On each admission he was aphasic and unable to swallow, and hyperreflexic on the left, with a left-sided weakness. Although jacksonian convulsions and semiconsciousness were present on admission to the Emergency Room, gradual recovery occurred. Laboratory data were always normal. Despite these periods of disability, the patient continued to work as a message runner for Western Union.

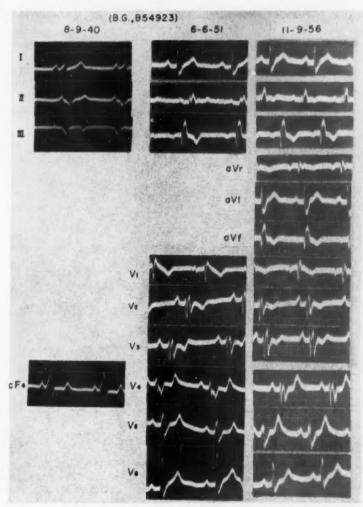


Fig. 1. Record of August 9, 1940, shows slurred R (delta) wave with QRS 0.12 sec. (Wolff-Parkinson-White); records of June 6, 1951, and November 9, 1956, exhibit right bundle branch block.

During an admission in 1940 an apical systolic murmur was described and attributed to rheumatic mitral valvular disease. The electrocardiogram (figure 1) showed anomalous A-V conduction typical of Wolff-Parkinson-White syndrome. In 1951 and 1956 a prolonged P-R interval and an intraventricular conduction defect with right bundle branch block were noted. Severe cardiomegaly was present in 1951 on roentgenologic examination (figure 2).

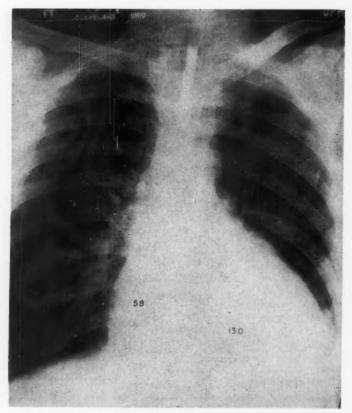


Fig. 2. Posteroanterior view, showing marked cardiac enlargement, normal aorta and relatively clear lung fields.

In 1957 the patient was admitted with signs and symptoms of intestinal obstruction. A portion of the small intestine was resected because of mesenteric thrombosis, but he deteriorated rapidly, death occurring on the seventh postoperative day. It was not until the last admission, at a time when his general condition was too precarious to permit critical study, that a diagnosis of Ebstein's anomaly was suspected. Necropsy substantiated the provisional diagnosis and showed multiple infarctions of various ages in the brain, liver, kidneys and spleen. The heart weighed 665 gm., and the major portion of the mass was right atrium and right ventricle.

DISCUSSION

Various descriptions of the embryology and pathology of Ebstein's anomaly have been proposed.¹⁰ Reported necropsies emphasize that any explanation should account for all components of the tricuspid orifice—leaflets, papillary muscles and chordae. There is variation between reported cases, but the anterior leaflet is most apt to be in normal position, with the posterior leaflet arising well below the annulus; the medial leaflet is likely to be a fenestrated,

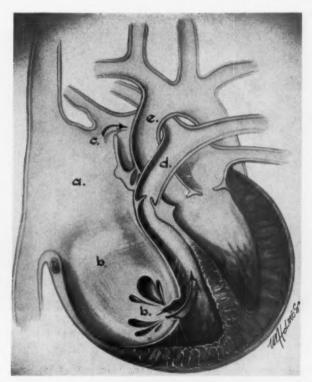


Fig. 3. Semidiagrammatic sketch: (a) right atrium; (b) atrialized portion of right ventricle and fenestrated displaced valve; arrow indicates small functional right ventricle; (c) atrial septal defect or patent foramen ovale; (d) pulmonary artery; (e) aorta.

"sail-like" flap, and all leaflets may be fused and appear to hang down into the ventricle like a basket. As a result of the displacement of the valve there is a large right atrium, with atrialization of a portion of the right ventricle of varying size, with a grossly deformed and small, functional right ventricle. An interatrial septal defect is frequently present. The left side of the heart is most often normal 11 (illustrated semidiagrammatically in figure 3). Figure 4 is the heart of our patient, showing the opened right atrium and right ventricle. Probe patency of a foramen ovale is present. As a result of these abnormalities, the

output of the right ventricle and the pulmonary blood flow is decreased. As the right atrium becomes distended and less able to empty, the right atrial pressure is increased and the foramen ovale may become patent.

Symptomatically, in the adult, the ability to continue activity may be a characteristic feature, as illustrated by our patient, who carried messages until shortly before death. However, dyspnea may occur and may be severe on exertion. Distress from arrhythmias has been described, 12 as they are frequent in this anomaly, and it is possible that our patient had his convulsions and perhaps even his original fall on the basis of a paroxysmal arrhythmia.



Fig. 4. Heart showing posterior, medial and anterior surfaces of right ventricle and right atrium. White cord (a) indicates tricuspid ring; black cord (b) outlines insertion of valve leaflets.

Physical examination may be misleading. The heart sounds are usually of poor quality, with systolic, presystolic or mid-diastolic murmurs at or near the apex of the heart. These murmurs may be misinterpreted as an indication of rheumatic mitral valvular disease, for as the right atrium and atrialized portion of the right ventricle become large, the tricuspid orifice moves to the left, probably causing the murmurs to be heard at the apex.¹² Pulsating liver or neck veins, though described in patients with failure, are not common in adults. Cyanosis, common in infants, is rare in adults, and may be confined to the terminal stages.

The electrocardiogram has been emphasized in the literature. Van Lingen and Bauersfield ¹³ have reported data on eight cases (three necropsied), and believe there is a pattern sufficiently distinctive to be of diagnostic value. Their characterizations consist of complete or incomplete right bundle branch block,

small deflections of R and RS in Lead V_1 , and commonly in V_2 , V_3 , and V_4 , and large amplitude and an increased duration of the P waves with a prolongation of the P-R interval. In addition, they believe the small R or R' deflections in the chest leads are in contrast to the usual right bundle branch block, where the R waves usually exceed those taken over the left precordium. Lev and others reported that ectopic paroxysmal tachycardia may result from the sometimes associated Wolff-Parkinson-White syndrome. Furthermore, Sodi-Pallares believes that type B Wolff-Parkinson-White syndrome in a patient with suspected congenital heart disease "obligates one to think of Ebstein's disease." He has never seen Wolff-Parkinson-White syndrome with cyanosis except with this anomaly.

As illustrated in figure 1, the series of electrocardiograms of our patient extend over a period of 16 years. Originally the record showed anomalous A-V conduction with a definite delta wave of Wolff-Parkinson-White syndrome. This anomalous A-V conduction disappeared, and in 1951 the electrocardiogram assumed the "characteristic pattern." Obviously, Ebstein's anomaly was present in 1940 at the time of the first electrocardiogram. The sequential changes shown by the series of electrocardiograms of our patient seemingly would indicate that a "characteristic pattern" of Ebstein's anomaly represents only fortuitous observations.

Roentgenograms (figure 2) and fluoroscopy of the heart offer the most specific diagnostic features of the usual methods of examination. The heart may be grossly enlarged and tend to have a narrow-waisted globular appearance in the adult. The left border may be slightly convex and elevated, and the pulmonary vascular markings should be diminished. The right side is usually markedly enlarged, with relatively little pulsation, and the pulmonary artery and aortic arch are normal or small.

Correct antemortem diagnoses have been made by employing cardiac catheterization and angiography.⁶⁻⁷ The catheter usually coils in a large right atrium and may cross an associated interatrial septal defect. There is difficulty traversing the tricuspid valve, which is displaced to the left; arrhythmias, potentially dangerous, occur frequently. The pressures in the right ventricle and pulmonary artery are normal, though they may be elevated in the right atrium. Angiocardiography demonstrates an enlarged atrium, with slow emptying, and the functional right ventricle, if seen at all, is small. Although such findings would seemingly be characteristic, and the above diagnostic measures indicated, deaths have been reported in cases of Ebstein's anomaly from each of these procedures.¹⁶

The course of these patients may show marked variations. They may enjoy active lives and die of unrelated disease. Congestive failure may supervene, and fatal cerebral embolization may occur through the associated interatrial defect. Sudden unexpected death has been attributed to the paroxysmal arrhythmias. Malan 9 in 1908 reported the case of a 60 year old white male with Ebstein's anomaly who had multiple splenic and hepatic infarcts and thrombosis of the right iliac and mesenteric arteries. Similarly, our patient had infarctions of brain, liver, spleen, kidney and mesenteric arteries. Possibly paroxysmal arrhythmias decrease cardiac output sufficiently that thrombo-embolism with infarction occurs.

In summary, an adult case of Ebstein's anomaly may have a fairly good exer-

cise tolerance, occasionally experience paroxysmal arrhythmias, have a markedly enlarged heart almost entirely involving the right side, with diminished pulmonary vascular pattern, and an abnormal electrocardiogram with conduction defect of the Wolff-Parkinson-White or right bundle branch block type. There may be catheter and angiocardiographic evidence of an enlarged right atrium with a small right ventricle.

As the clinical picture of any anomaly is appreciated, the reported incidence increases. With this in mind, an attempt has been made to emphasize the diagnostic features of Ebstein's anomaly and to stress the fact that the correct diagnosis of the classic case should be established, particularly in the adult.

SUMMARIO IN INTERLINGUA

Un congenite anormalitate, consistente del displaciamento in basso del valvula tricuspide, esseva describite per Ebstein in 1866. In recente annos, plure exhauriente articulos relative a iste anormalitate ha essite publicate con collectiones de casos, e il ha occurrite que le diagnose del condition esseva facite correctemente durante le vita del patiente. Adams e Hudson ha reportate le caso de un patiente supervivente al etate de 79 annos, e nostre patiente moriva al etate de 60 annos (apparentemente in consequentia de un morbo non affin), sed a generalmente parlar le casuistica in le litteratura sublinea le characteristicas de iste anormalitate in patientes de etate infantil.

Yater, Soloff, Van Lingen, Blount, e alteres ha establite un schema specific pro le diagnose clinic. Le signos physic pote esser confundite con illos de rheumatic morbo mitral, sed le constatationes roentgenoscopic offere plus frequentemente indicios pro le diagnose. Isto esseva ver in le caso de nostre patiente. Infelicemente, on ha troppo sublineate le signos electrocardiographic, opinante que illos es characteristic. Le electrocardiogrammas de nostre patiente, coperiente un periodo de 16 annos, revela alterationes que representa solmente verso le fin le disposition de signos que ha essite designate como "typic."

In tanto que le tableau clinic de un anormalitate de non importa qual genere es recognoscite plus clarmente, le reportate incidentia de illo tende a crescer. In consideration de iste facto, le presente articulo es publicate pro sublinear le aspectos diagnostic del anormalitate de Ebstein de maniera que le correcte diagnose del caso classic, specialmente in le patiente adulte, pote esser facite plus frequentemente.

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RENAL INVOLVEMENT IN SCLERODERMA*

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Although it is well recognized that scleroderma is a generalized disease, the specific pathologic changes in the kidneys have only recently been emphasized. In 1952 Moore and Sheehan described the lesions in the renal cortices of three patients dying from renal involvement by scleroderma. Since then several reports have stressed renal involvement as a cause of death in scleroderma. Since then the several reports have stressed renal involvement as a cause of death in scleroderma.

The following case, together with a summary of cases reported in the English literature, illustrates the striking similarity in clinical course and pathologic findings. Only cases with adequate descriptions of clinical course and autopsy findings have been included in the summary.

CASE REPORT

First Admission: A 56 year old white man was first admitted to the hospital on October 6, 1958, with the complaints of stiffness and weakness of his shoulders and hands. He had first noticed this weakness when using a drill press, which had grown heavier for him until he was unable to lift the instrument. He had also noticed a tightness of his skin which made it difficult for him to close his fist. He denied any

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difficulty in swallowing, and had never noticed any blanching or redness of his fingers upon exposure to cold.

Past History: The patient had had good health during his youth. In 1900 he had been operated upon for an appendiceal abscess. In 1944 he had suffered an episode of joint pain involving both elbows, which became erythematous and warm. A private physician treated him with gold injection and later with x-ray.

Physical Examination: Blood pressure, 120/66 mm. of Hg; pulse, 88 and regular; temperature, 100° F. (oral). The patient's face was masklike. The shoulder muscles were wasted, and the fingers of both hands were clawed and held in flexion. The skin over the hands and forearms was tight and indurated. There was limitation of movements of the wrists, fingers and shoulders, with crepitation in the involved joints when the limbs were moved passively. No loss of hair was observed in the affected area. Examination of the fundi showed slight arteriolar constriction, without any exudates or hemorrhage. The lung fields were clear. The point of maximal impulse of the heart was in the fifth intercostal space, 8 cm. to the left of the midsternal line. No murmurs were heard. No abnormal organs or masses were palpable in the abdomen. Two well healed surgical scars were found in the right lower quadrant. The skin over the lower extremities was tight and shiny.

Laboratory Examination: Hemoglobin, 12.4 gm.; hematocrit, 38; white blood cells, 10,450, with a normal differential. Sedimentation rate: 33 corrected, 50 uncorrected. Urinalysis showed a specific gravity of 1.025, with no albumin, sugar or cellular elements. The result of the serologic test for syphilis as performed with the Venereal Disease Research Laboratory (VDRL) antigen was negative. Two L.E. cell preparations were negative. Total protein was 6.3 gm., with an albumin of 3.73 and globulin of 2.57. Chest x-ray showed no active lung disease, and the cardiac configuration was normal. An upper gastrointestinal series revealed no abnormality of the esophagus. A biopsy of the skin over the dorsum of the hand was diagnostic of scleroderma.

Course: On October 23, 1958, the patient was started on Meticorten, 5 mg. every six hours for a week, with gradual reduction of dosage until he was discharged on 2 mg. four times a day. Throughout his hospital stay there was no improvement in the stiffness of his joints. During November, 1958, he was followed in the out-patient clinic, where physical therapy to his joints seemed to be of distinct value. On December 31, 1958, he complained for the first time of loss of appetite, nausea and vomiting, and also of edema of his face and legs. Meticorten was then discontinued.

Second Admission: On January 11, 1959, the patient came to the emergency ward in acute pulmonary edema. For the week before this second admission he had become short of breath after walking a few steps, and could not climb a flight of steps without having to stop for breath. On the night of admission he had had a sudden onset of severe shortness of breath and had begun to cough up bright red blood in his sputum. There was no associated chest pain.

Physical Examination: Blood pressure, 200/130 mm. of Hg; pulse, 200 and regular. The patient was severely dyspneic and orthopneic. His extremities were cold and clammy. Examination of the fundi revealed fresh hemorrhage and exudate in the left. He had marked venous distention, and there were inspiratory and expiratory wheezes and râles in both sides of the chest. Precordial activity was marked, with the point of maximal impulse in the anterior axillary line, fifth intercostal space. The rhythm of the heart was extremely rapid and tictac in character. No murmurs were heard. There was pitting edema bilaterally in both lower extremities. No abdominal organs were felt.

The patient was treated with morphine, oxygen, intravenous aminophylline and a rotating tourniquet, without much improvement. A phlebotomy of 500 c.c. and

intravenous digitalization were performed. An hour after medication the pulse rate slowed to 100 and the blood pressure dropped to 160/100 mm. of Hg.

Laboratory Studies: Hemoglobin, 10.5 gm.; white blood cells, 15,650, with 82% polymorphonuclears and 18% lymphocytes; red blood cells, 4,500,000. Urinalysis showed a specific gravity of 1.018, with 4 plus albumin, no sugar, and two to six white blood cells and 20 to 30 red blood cells per high power field. Blood urea nitrogen was 47. An electrocardiogram showed sinus tachycardia. Chest x-ray revealed a markedly-enlarged heart, with a transverse cardiac diameter of 19 cm. over a transverse thoracic diameter of 31 cm. The lower two thirds of both lung fields were occupied by fluffy multiple densities having the appearance of pulmonary edema. Serum glutamic oxalacetic transaminase (SGOT), 20 and 28 units. Total protein, 7.2; albumin, 3.57 and globulin, 3.63.

Course: The patient became progressively oliguric and finally anuric a week after admission. Blood pressure readings remained around 180/110 mm. of Hg until the terminal stage. A pericardial friction rub was heard on January 17, 1959, and definite uremic frost appeared over the face and body on January 20. The next day the patient died quietly. Below is a record of urine output, specific gravity and blood urea nitrogen determinations.

| Date | Blood Urea Nitrogen | 24-Hour Urine Output (in c.c.) | Sp. Gr. |
|---------|---------------------|-----------------------------------|---------|
| Jan. 11 | 47 | _ | 1.018 |
| Jan. 12 | 87 | _ | - |
| Jan. 13 | 123 | 300 | 1.015 |
| Jan. 16 | 159 | 250 | 1.013 |
| Jan. 19 | 261 | 30 | _ |

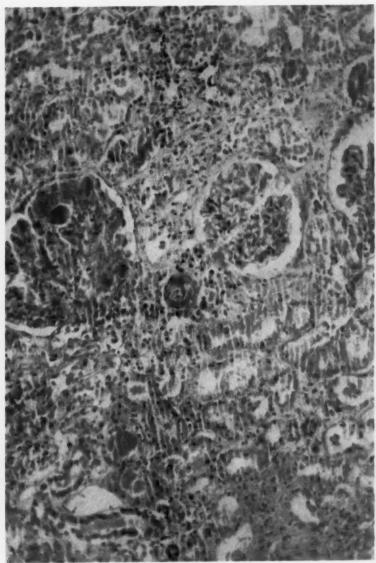
On autopsy, each kidney weighed 210 gm. Numerous petechiae and small ecchymoses were present over the surfaces of the kidneys, which were coarsely granular. Small, pale, irregular areas, measuring approximately 0.3 cm. in diameter, were scattered over the surfaces of the kidneys, forming a mosaic pattern. On sectioning, the cortex of each kidney measured 0.5 cm. in thickness. Petechiae and small ecchymoses were present in the cortices; these were interspersed with pale areas similar to those seen over the external surfaces. The pyramids were dark red. Microscopically, the cortex of the kidney contained numerous small infarcts. The parenchyma bordering these infarcts was infiltrated by numerous neutrophils; this infiltrate was primarily between the uriniferous tubules. Almost all of the small and medium sized arteries were altered. There was a diffuse proliferation of connective tissue in the intima and media of the interlobular arteries. Fibrinoid necrosis was present in the afferent arterioles, and extended into the entire glomeruli in many areas. There were a few recent thrombi in some of the arterioles. The basement membranes were thickened in some of the glomeruli. The epithelial cells in most of the tubules were atrophic. Occasional nuclei were absent in the tubular epithelium.

Random sections of the skin taken at autopsy from the abdomen and anterior chest revealed the typical changes of scleroderma. The esophagus microscopically showed slight involvement by this disease. There was an increase in connective tissue around the terminal portion of the esophagus, replacing some of the smooth muscle.

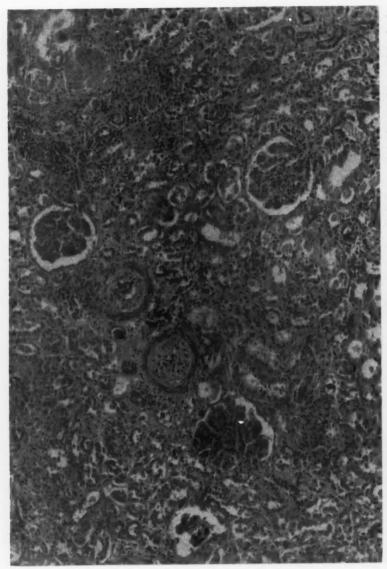
The heart was enlarged, weighing 480 gm. This enlargement was due mainly to an increase in the size of the left ventricle, which measured 2 cm. in thickness. There was a slight increase in the interstitial connective tissue. Arterioles in the myocardium were normal in appearance. The interstitial fibrosis was no greater



Photomicrograph of a section of kidney. Note the irregular zone of coagulation necrosis in the lower portion of the picture. The infiltrate between the tubules is made up primarily of neutrophils. Frg. 1.



Photomicrograph of the kidney, showing fibrinoid necrosis in the arteriole. The fibrinoid necrosis and thick-ening of the vessel wall extend out into the glomerulus in the upper part of the picture. 2



Photomicrograph of a section of kidney. There is fibrous intimal thickening of the interlobular arterioles in the upper central portion of the picture. Note the fibrinoid necrosis in several of the glomeruli.

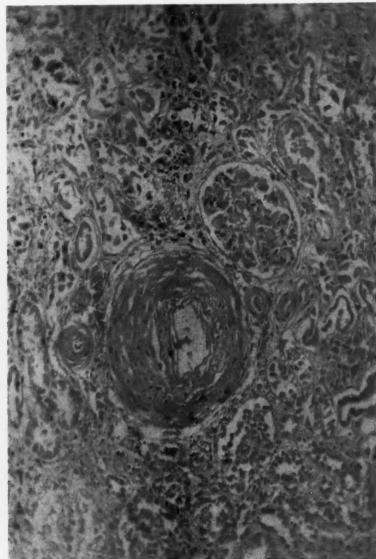
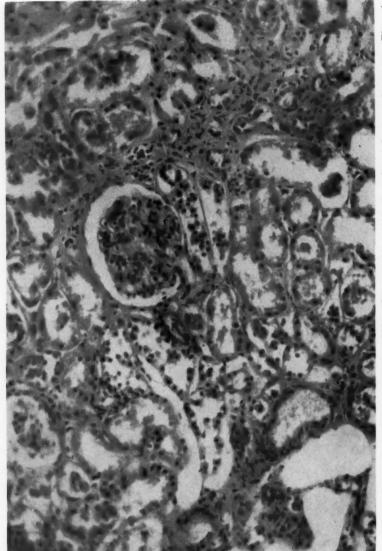


Fig. 4. Photomicrograph from a section of kidney from a patient with malignant arteriolar nephrosclerosis. The interlobular artery shows fibrous intimal thickening, in this case involving the media also. There are fibrinoid necrosis of the arterioles and also a thickening of the walls of the capillary loops in the glomerulus.



Fro. 5. Photomicrograph of a section of kidney from a patient with disseminated lupus erythematosus. There is some thickening of the walls of the glomerular capillaries. The arterioles and the interlobular arteries were not abnormal in the kidney in this case.

TABLE 1
Cited by Moore and Sheehan 1

| Source | Age | Sex | Blood Pressure (mm. of Hg) | Renal Function | Renal Lesion | |
|------------------|------------|------------|-------------------------------|---|--|--|
| Masugi and Va | 23 | F | 100/80 | Normal | Fibrinoid changes in intralobular arteries and atypical intimal thickening | |
| Talbott et al. | 27 | F | Normotensive | Normal until one week before death | Characteristic renal lesion with much no crosis of parenchyma | |
| B. M. Banks | 51 | F | 95/60 | Slight albuminuria 5 days before death | Intralobular arteries showed fibrinoid changes but no intimal thickening | |
| Weiss et al. | 56 | F | 160/110 | No record of renal in- sufficiency | Intralobular arteries showed intimal thick- ening but no fibrinoid necrosis | |
| M. Bevans | 36 (Cas | F se 1) | 112/80 | Gross albuminuria; blood urea nitrogen (BUN), 35 mg.% | Characteristic renal lesions with some wireloop in glomeruli | |
| | 56 (Cas | F ie 2) | 130/80 to 158/100 | BUN, 43 mg.% | Characteristic renal lesions with some wireloop in glomeruli | |
| R. H. Goetz | 44 | F | 100/65 | No information | Characteristic lesion | |
| Platt and Dawson | 40 | F | Hypertensive | Uremia; BUN, 145 mg.% | Characteristic lesion | |

Table 2
Patients with Renal Failure Who Had Not Received Steroids

| Source | Age | Sex | Blood Pressure (mm. of Hg) | Renal Function | Renal Lesion |
|--|------------------|------------|---------------------------------------|---|--|
| Moore and Sheehant | 54 F (Case 1) | | 140/80 | before death necrosis. Proximal intr | All three cases showed focal cortical necrosis. Proximal intralobular arteries with intimal thickening |
| | | M se 2) | 130/85 | No information | Distal intralobular arteries and afferent arterioles showed fibrinoid necrosis |
| | 38 (Ca: | F se 3) | 165/100 | Normal until 3 weeks before death; blood urea nitrogen (BUN), 260 mg.% terminally | MCG VSIS |
| Hannigan et al.º | 26 | F | 96/60 240/150 (terminal) | Urine normal until 2 weeks before death in uremia | Patchy cortical necrosis. Interlobu- lar arteries showed fibrous thicken- ing of intima. Distal portion of interlobular arteries showed fibri- noid necrosis |
| Rodnan et al.ª | 55 (Cas | M se 4) | 120/70 220/120 (1 month later) | 1 + albuminuria; BUN, 44 mg.% | Cortical infarcts. Necrosis of ar- teriole wall. Sclerosis of inter- lobular arteries |
| CPC case #43341.5 New England J. Med. | 29 | F | 108/64 210/130 (2 months later) | 1 + albuminuria; nonprotein nitro- gen (NPN), 37 mg.% | Focal hemorrhage of cortex. Fibri- noid necrosis of arterioles |
| CPC case, 12 Am. J. Med. | 49 | F | 120/65 190/100 (2 months later) | Normal urine; BUN, 19 mg.% | Focal infarcts. Intralobular arteries with fibrinoid necrosis |
| Mathisen and Palmer ¹³ | 23 | F | 106/75 | Faint albuminuria; BUN, normal | Focal cortical infarcts. Wireloop glomeruli |
| CPC case #42211,14 New England J. Med. | 57 | F | 240/129 | 2 + albuminuria; BUN, 100 mg.% | Cortical necrosis. Fibrinoid necrosis of arterioles |

than would be expected in a heart of this size. Minimal arteriosclerosis of the coronary arteries was present.

The remaining findings were terminal changes due to uremia and congestive heart failure. There was passive congestion of the lungs, liver and spleen. A pericardial effusion of 300 ml. and a pleural effusion of 300 ml. on the left were present. A small amount of altered blood was found in the small intestine. There were a few small, scattered hemorrhagic areas in the lungs. An acute pancreatitis of moderate degree was also present.

Table 3
Patients with Renal Failure Who Had Received Steroids

| Source | Age | Sex | Blood Pressure (mm. of Hg) | Renal Function | Renal Lesion |
|---------------------------|------|-----------|---------------------------------------|--|---|
| | 66 | М | 180/85; terminal, 210/120 | 2+ albuminuria; blood urea nitrogen (BUN), 69 to 180 mg.% | Cortical infarcts. Intimal thickening of interlobular arteries. Necrosis of af- ferent arterioles |
| | 44 | F | 132/74 | Urine, normal; BUN, 41 mg.% | Necrosis and thrombosis of intrinsic ar- teries and afferent arterioles. Focal necrosis of glomeruli and degeneration of tubules |
| | 26 | F | 100/60 | Urine, normal; later, 3+ albuminuria; BUN, 141 mg.% | Extensive necrosis and thrombosis of smaller renal arteries and focal cortical necrosis |
| | 47 | F | 130/85 | Urine, normal; BUN, 33 mg.%; 4+ albuminuria and BUN, 211 mg.% terminally | Subcortical hemorrhage. Intimal pro- liferation and thickening of arteries and arterioles. Fibrinoid necrosis |
| | 45 | F | 180/110 | 1 to 3 + albuminuria; broad renal failure; casts; BUN, 74 to 167 mg.% | Extensive necrosis of afferent arterioles. Intimal thickening of interlobular ar- teries. Areas of cortical infarcts |
| Fred and Rambo4 | 39 | M | 120/75; 3 months later, 190/120 | Normal urine; ter- minal BUN, 260 mg.% | Cortical infarcts. Intimal fibrosis of in- terlobular arteries. Fibrinoid necrosis of afferent arterioles |
| Lunseth et al.4 | 48 | M | No information | Normal until 4th day of treatment, BUN then 134 mg.% when patient was anuric | Cortical necrosis. Intimal fibrosis of in- terlobular arteries. Fibrinoid necrosis of afferent arterioles and glomeruli |
| Sharnoff et al.10 | 41 | F | 100/70; terminal, 220/120 | Normal urine; BUN, 16 mg.% | Infarcts in cortex. Intimal fibrosis of interlobular arteries |
| Zarafonetis ¹⁵ | (Cas | M e 4) | 110/60; 6 wks. later, 180/124 | No record | Fibrinoid necrosis of arterioles and glo- meruli. Cortical necrosis |
| Calvert and Owen16 | 57 | F | 130/70 | Albuminuria; BUN, 24 mg.%; 1 month later, 216 mg.% | Focal cortical necrosis. Intimal proliferation of interlobular arteries |

Discussion

The present case illustrates the following significant features: (1) early in the course of the disease, most cases of scleroderma, like our case, do not exhibit any evidence of hypertension; 1, 7, 8 (2) also, renal involvement is not clinically demonstrable early in the illness. 1, 9 But once renal symptoms develop, the disease progresses to a quick, fatal conclusion. It has been suggested that the use of steroids hastens the onset of renal failure in some patients. 1, 10 However, prior to the introduction of steroids, patients with scleroderma succumbed quickly

with uremia as a result of renal involvement by the disease process.^{1, 3} (Compare tables 1 and 2 with table 3.)

The findings in the kidneys in our case of generalized scleroderma were similar to those reported by others. This disease produces a specific pathologic pattern in the kidneys, characterized by focal necrosis in the cortex, fibrosis of the intima of the interlobular arteries, fibrinoid necrosis of the arterioles, and thickening of the basement membrane of the glomeruli. The concentric fibrosis of the intima of the interlobular arteries occasionally involves the media also.

Although Moore and Sheehan ¹ considered the renal lesions in scleroderma to be specific, Fisher and Rodnan ¹¹ stated that the lesions were morphologically and tinctorially indistinguishable from those seen in malignant nephrosclerosis. Slides of the kidneys of 15 patients who died from malignant nephrosclerosis at this hospital were reviewed, and all showed fibrinoid necrosis in the arterioles. There was fibrosis of the media and intima of the interlobular arteries. Degenerative changes in the tubular epithelium were present in all of the cases. There was also thickening of the basement membrane of the glomerular capillaries. These changes were identical with those seen in our autopsied case of scleroderma. However, in no case of malignant nephrosclerosis was there any gross or microscopic evidence of cortical infarction, which was seen in our case and other reported cases of scleroderma (tables 1, 2 and 3). In most of those cases in which cortical necrosis was not reported, the kidneys did show focal or diffuse cortical hemorrhages.

Thickening of the basement membrane in the glomeruli in generalized scleroderma is similar to that seen in disseminated lupus erythematosus. Four patients with disseminated lupus erythematosus have been autopsied in this hospital. Microscopic changes in the kidneys in these cases were far less dramatic than those seen in generalized scleroderma. In the cases of disseminated lupus erythematosus there was some increase in cellularity, in addition to thickening of the basement membrane of the glomeruli. However, the arterioles did not show fibrinoid necrosis, nor were the interlobular arteries involved.

SUMMARY

A case has been presented of generalized scleroderma with particular reference to the kidney lesions. The kidney lesions in this disease constitute a specific pattern, characterized by multiple cortical infarcts, fibrous thickening of the interlobular arteries, fibrinoid necrosis of the arterioles, and thickening of the basement membrane of the glomeruli. In those cases not showing multiple cortical infarcts, cortical hemorrhages are present. This pattern is distinguishable from that seen in malignant nephrosclerosis and disseminated lupus erythematosus.

An additional point of interest was found on reviewing the literature. Once evidence of renal involvement develops clinically, the disease progresses rapidly to a fatal conclusion. This same pattern was noted both in cases that had and in those that had not received steroid therapy.

SUMMARIO IN INTERLINGUA

Es reportate le caso de un masculo blanc de 56 annos de etate qui moriva del affection renal per scleroderma. Es summarisate le datos necroptic de patientes con

affection renal per scleroderma in tanto que illos es reportate in le litteratura de lingua anglese.

Le casos summarisate super le base del litteratura e le caso hic reportate revela frappante similitudes in le curso clinic. Etiam le constatationes pathologic facite al necropsia es simile.

Patientes con scleroderma non ha clinicamente demonstrabile lesiones renal in le stadios precoce del curso de lor morbo. Si tosto que symptomas renal se disveloppa, le morbo progrede rapidemente verso su conclusion mortal. On has exprimite le suspicion que le uso de steroides accelera le declaration del disfallimento renal. Tamen, precisemente le mesme curso clinic esseva observate in le caso de patientes qui non se trovava sub therapia a steroides.

Le lesiones renal forma un configuration specific, que es characterisate per multiple infarcimentos cortical, spissification fibrose del arterias interlobular, necrosis fibrinoide del arteriolas, e spissification del membrana basal del glomerulos. In le casos que non exhibi multiple infarcimentos cortical, hemorrhagias cortical es presente. Iste configuration es distinguibile ab illo incontrate in nephrosclerosis maligne e in disseminate lupus erythematose.

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EDITORIAL

THE PROBLEM OF RES IPSA LOQUITUR*

A MALPRACTICE suit against a physician is a civil action based on allegations by the plaintiff that the physician was negligent in making the diagnosis or in prescribing or implementing the treatment. In our system of jurisprudence, in the United States, the plaintiff must prove by expert medical testimony that the defendant failed to exercise reasonable care or skill and therefore is liable for damages. Testimony of the expert witnesses, both of the plaintiff and of the defendant, is heard by the jury, which then reaches its verdict after weighing the medical opinions and other evidence.

The requirement that medical evidence be supported by expert testimony is subject to at least one exception; the doctrine of *res ipsa loquitur*—"the act speaks for itself." Invoking this doctrine may relieve the plaintiff of the burden of supporting his allegations by medical experts. The burden of explaining the then legally inferred medical negligence rests upon the defendant-physician. The court turns to the defendant-physician: "Doc-

tor, explain why you amputated the wrong leg."

Were the application of the doctrine of res ipsa loquitur as simple as this illustration, little objection would be raised in applying it to medical malpractice actions. The surgeon (if he did so in fact) cannot deny that he amputated the wrong leg, extracted the wrong tooth, removed the one remaining kidney. These acts of negligence are clearly within the common knowledge of the jury. However, legal procedure permits the defendant to explain any mitigating circumstances. In law, this is stated: the burden of going forward with the evidence shifts to the defendant. The burden of proof still remains on the plaintiff to show the jury that the physician was negligent, but the physician is now given an opportunity to tell his story of non-negligence.

Criticism arises when the doctrine of *res ipsa loquitur* is applied (in some jurisdictions) to cases of malpractice in which the medical negligence is not within the common knowledge of the jury. That is, when the controversy involves the exercise of reasonable *skill*. Here, then, is the area of conflict where legal and medical authorities differ in the application of the doctrine

to malpractice suits.

When a patient consults a physician, a contract arises between both parties. Collateral to the obligations of contract between the physician and

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From the Department of Anesthesiology, The Cleveland Clinic Foundation, and The

his patient, the law imposes the implied obligation to exercise reasonable care and skill. Failure to exercise reasonable care or reasonable skill is basic to the successful prosecution of a malpractice action. "Reasonable skill" is defined as that degree of skill exercised by the average physician of the same specialty in the same or similar locality. It does not mean the highest degree of skill, because the law does not require a physician always to be best or at his best. The proof of dereliction in the defendant's duty to exercise reasonable care or skill, ordinarily requires that the plaintiff procure the expert testimony of another physician. This is a safeguard the law has created to protect the defendant-physician and to prohibit the jury's speculating over medical matters not within their common knowledge. Without expert testimony, in almost all cases, the plaintiff must fail.

The plaintiff's expert usually states an opinion concerning a hypothetical question based on the situation in the case. If the plaintiff's and the defendant's experts do not agree, this conflict of medical opinion constitutes the issue of fact for the jury to decide. They place the evidence on the scales of justice to determine who is favored by the greater weight of the evidence. Although science has questioned this particular method of meting out justice, it must be recognized that the law is attempting to find a solution to an existing dispute between two parties, not an absolute rule of scientific certainty. An immediate answer is required. The medical mind finds it difficult to comprehend such a procedure fully. Not only is the courtroom a strange mise en scène, but the lawyers' seemingly semantic manipulation of issues of law and fact does violence to the physician's sci-

entific concept of a quest for objective truth.

When res ipsa loquitur is applicable to malpractice actions, the plaintiff merely states that the defendant-physician was in the exclusive control of the instrumentality causing the injury and that such injury does not usually occur unless the instrument was negligently used. This creates for the jury (by the laws of evidence), a possible inference of negligence by the defendant; and the jury then may, or may not draw such inference. The court, thereby, may excuse the plaintiff from procuring expert medical testimony to establish the precise act of negligence. It is interesting, however, that res ipsa loquitur has been applied most commonly in medical situations where the absence of the required amount of care, not of skill, was the grounds of negligence. Although many jurisdictions apply res ipsa loquitur to the former, few courts will apply res ipsa loquitur to medical malpractice based on lack of the requisite amount of skill. Lack of care is usually within the common knowledge of the jury; lack of skill ordinarily stands only on expert medical testimony because it deals with scientific fact, judgment, and experience.

When res ipsa loquitur is applied, the rules of evidence create only an inference (not a presumption) that the defendant was negligent. That is, the defendant, at first blush, is to be considered negligent by the jury. But

even the possible inference is not binding on the jury. Should they accept the explanation of the defendant, or not be satisfied with the factual evidence, the inference of negligence by *res ipsa loquitur* is overcome. More significant, however, may be the glaring deficiency in evidence in the plaintiff's case. The application of the doctrine decreases the actual amount of testimony in the plaintiff's case. The amount of testimony required by the defendant to overcome the plaintiff's case is, therefore, less. *Res ipsa loquitur* is not a one-way street to absolute medical liability.

Some courts do apply res ipsa loquitur to medical malpractice actions involving skill. Expert medical testimony by the plaintiff is then excused, and an inference of the defendant's negligence is created for the jury. This permits the jury to speculate with highly technical scientific facts wholly within the understanding of a physician. How can a lay jury determine whether or not the medical act of the defendant was negligent? Medical experts often cannot agree, yet the court asks the lay jury to determine whether or not the explanation by the defendant overcomes the inference

of negligence at law.

Originally, the doctrine of res ipsa loquitur was applied to such situations as a train wreck or a streetcar accident in which the passenger was hurt. The passenger had no way of knowing whether the engineer of the train was operating the train negligently. The plaintiff said in his case that the instrumentality was wholly in the control of the defendant and that trains do not usually get wrecked unless negligence is present. In malpractice, we are dealing with the practice of an inexact science, not the operation of a streetcar or a train. How can the jury balance an inference (created by the law of evidence) against the intangibles of medical practice? As Professor Prosser stated, it is an attempt to compare a dozen oranges with half past two o'clock. Can the jury in good faith come to a logical conclusion? Or is this a case of the "rule of sympathy"? Does the party who wins the greatest amount of sympathy of the jurors receive the verdict, and does the application of the rule merely provide the means to reach such a "sympathy verdict"? In these circumstances, res ipsa loquitur is an unreasonable courtmade rule creating evidence.

Historically, the courts have protected the practice of medicine from legal assault. Plaintiffs-to-be have many hurdles to overcome before they may successfully prosecute a negligence action against a physician. Then, why have the courts applied the doctrine of res ipsa loquitur to medical malpractice cases? One answer is found in the decision of a California court which openly criticized the medical profession for entering into a "conspiracy of silence." This same court stated that the requirement of expert medical testimony to support the plaintiff's claim is a rule to protect the physician from unjust prosecution. The court insisted that medical facts are too complex and that the jury should not be permitted to speculate as to medical matters. However, when the plaintiff is unable to procure the services of

any medical expert, he usually fails to establish a case in malpractice. Missing are the necessary basic requirements of a negligence action—the testimony establishing the standard of care and the breach of that standard. The plaintiff is then defeated by a court-made rule devised solely for the protection of the defendant-physician. Recognizing this refusal of physicians to testify for the plaintiff (thus converting a legal defense into an offensive weapon) as a "conspiracy of silence," the courts countered by modifying the rules of evidence. Thus, by a legal manipulation, the basic rules of negligence, while not changed, were dispensed with for the purposes of the Where the instrumentality causing the injury is in the exclusive control of the physician, and where it usually does not cause such injury unless carelessly used, and when no medical expert is procurable by the plaintiff. then let the defendant-physician explain his use of the instrumentality. He is an expert; he was present; he used the instrument; he had the duty to exercise reasonable skill. The court also, in effect, says to the jury: "The defendant, at first blush, is to be considered negligent, but, if he explains his actions to your satisfaction, then you may find in his favor." This, in legal parlance, is res ipsa loquitur, an inference of fact in favor of the plaintiff. It is overcome only by the defendant's satisfactory explanation of his actions.

With the application of *res ipsa loquitur*, the members of the medical profession find themselves in a difficult position. Traditionally being protected by the courts, they are now being criticized by the courts for interfering with the administration of justice. Most courts are sensitive to any interference with their judicial prerogatives. When the plaintiff exclaims that he is unable to find expert witnesses to appear for his cause, the court angrily retorts that this is a "conspiracy of silence" to protect an act of malpractice of another physician. Once established, the use of *res ipsa loquitur* in medical malpractice cases involving skill will inevitably spread to other jurisdictions. So far, it is well contained geographically.

If these charges by the courts are correct (and we must accept them as prima facie correct), our duty becomes self-evident. We must continue to protect the defendant-physician against unfounded charges of malpractice, but we must also provide experts for the plaintiff. It is not difficult to outline reasonable care and reasonable skill for the jury. If the defendant is clearly within these bounds, the jury will find for him. If he is without these legal boundaries, then the plaintiff has in law been injured. The courts demand that both sides of any controversy be heard. If the medical profession, in its "conspiracy of science" remains silent, the courts will speak for the plaintiff—res ipsa loquitur.

CARL E. WASMUTH, M.D., LL.B.

REVIEWS

Diseases of the Colon and Anorectum. Volumes I and II. Edited by ROBERT TURELL, M.D. 1238 pages (both volumes); 17.5 × 26.5 cm. W. B. Saunders Company, Philadelphia. 1959. Price, \$35.00 per set.

This two-volume treatise on proctology consists of a compilation of articles by both British and American authors, most of them general surgeons with an interest in this field, but with the help of a few proctologists. It has all the advantages and disadvantages of this type of publication. Although there is very complete coverage of the entire field, narrow though it is, the work loses the virtues of conciseness by reason of considerable overlapping of technical information, which the editor acknowledges.

The chapters do not confine themselves entirely to proctology as such. They cover many allied topics, the inclusion of which by various authorities adds to the adjunctive features of the subject. There are three chapters on electrolytes, and the injection treatment of hemorrhoids is treated as an item separate from diagnosis and surgical operations. One must observe, too, that the editor talks only of his own diagnostic and other instruments, which, good though they are, do not replace those of simpler construction in more common use.

In general, however, these shortcomings do not detract from the merit of the publication, in the assembling of which there is included much by the abler authors in this field from both sides of the Atlantic.

The illustrations are well selected, clear, and accurate and do much to elucidate the text.

If one can overlook the advantages of compactness, this may be considered an excellent reference book for the surgeon working in this or allied fields.

M. E.

Thyroid Radioiodine Uptake Measurement: A Standard System for Universal Intercalibration. ORINS-19, U. S. Atomic Energy Commission Report. By Mar-SHALL BRUCER, M.D. 323 pages; 26.5 × 20.5 cm. Oak Ridge Institute of Nuclear Studies, Inc., Oak Ridge, Tennessee. 1959. Price, \$3.50 (available from the Office of Technical Services, Department of Commerce, Washington 25, D. C.)

The author and his co-workers have done an outstanding job with an impossible problem.

The need for a book of this type was made apparent as far back as 1953 when it was learned at a national symposium that thyroid uptake measurements were being carried out by so many technics that standardization of procedure, exchange of data, and accuracy of results were impossible to ascertain. Moreover it was evident that most of the methods were scientifically inaccurate, and the test itself of no practical value except when clinical judgment was used in proper interpretation of the test data.

The results of a national survey, using standard manikins containing known amounts of radioactive iodine, emphasized the need for such standardization if the radioactive iodine uptake measurement were to be kept from falling into complete disrepute and in the very near future. Even in the best known laboratories results were obtained which were appallingly inaccurate.

The author undertook the task of working out a standard system using a simple procedure that would give a reasonably accurate measurement of thyroid radioiodine uptake. In his analysis of the various technics as many variables (patients, distances, filters, scalers, positioning, columnmation, spectra, etc.) as could be considered were

created and analyzed. All these factors are presented in a graphic, concise form so that the reader would be enlightened rather than confused by the mass of technical information.

This book is highly recommended to all who are interested in the measurement of radioactive iodine uptake by the thyroid gland as a test procedure.

R. E. B.

The Acute Medical Syndromes and Emergencies: Diagnosis and Treatment. By Albert Salisbury Hyman, M.D.; with the collaboration of Samuel Weiss, M.D., George Guttman Ornstein, M.D., Howard F. Root, M.D., Anna Ruth Spiegelman, M.D., and Jack Abry, M.D. 442 pages; 21 × 14 cm. Lansberger Medical Books, Inc., New York, N. Y. 1959. Price, \$8.75.

This is an extremely timely and valuable addition to that group of books handy to every physician whose daily practice may and does bring him unexpectedly to deal with the most common medical diagnostic and therapeutic emergencies. This is a small volume, but it is not suitable for carrying in one's pocket, and although it may easily fit into a medical bag, it is most likely to wind up on or near the doctor's desk or on the reference book shelf of a medical library where it will be easily accessible for quick reference.

In fact, this is truly a quick reference book. It deals mainly with the acute problems involving the heart, the gastrointestinal tract, the chest, and the lungs. Relatively less space is given to diabetic and renal emergencies and to barbiturate poisoning. Allocation of subject matter was made in accordance with results of a nation-wide poll in which physicians in active practice were asked to list the types of important acute medical problems which they had been called on to treat in the previous years. Detailed presentation of anatomic and physiologic subject matter was omitted on the assumption that the reader was familiar with the basic science aspects of the various syndromes discussed. On the other hand, the common problems in diagnosis and treatment are discussed broadly and in considerable detail when thought clinically important. Where life and death issues are involved in prompt and correct diagnosis and treatment, the authors spare no effort to clarify each problem. As may be expected, exactly half (214 of 427 pages) of the volume concerns itself with cardiovascular problems-angina in all its forms, myocardial diseases, conduction disturbances, and hypertensive and functional crises. Each topic is discussed in great clinical detail and nothing is left out which may help the physician to arrive at a rapid decision as to the proper diagnosis and treatment. Where there is difference of opinion as to treatment, as for instance in the question of anticoagulation, various views are given, but the authors leave no doubt as to what their own stand would be in any particular situation. All the drugs and dosages are given by name and various products are named, together with the name of the manufacturer of each. Forms of treatment other than medicinal are discussed and methods of use accurately outlined.

All in all, this is a most useful little book, which should be owned by any physician who ever finds the need for a quick and authoritative review of the diagnosis and treatment of the commoner medical emergencies.

L. V. B.

The Fluids of Parenteral Body Cavities. (Modern Medical Monographs 19. Editor-in-Chief: IRVING S. WRIGHT, M.D.; Consulting Editor: RICHARD H. ORR, M.D.)
By Paul D. Hoefrich, M.D., and John R. Ward, M.D. 98 pages; 22.5 × 14 cm. Grune & Stratton, Inc., New York. 1959. Price, \$4.75.

This is a concise, well written, meticulously organized, highly reliable monograph that concerns itself—as the title states—with fluid accumulations in parenteral body

cavities. In turn, the authors consider Serous Fluid, which they define as the liquid of the pleural, pericardial and peritoneal cavities; Synovial Fluid; and Cerebrospinal Fluid.

Each of these is discussed with discrimination under a rigidly followed outline: Introduction, Anatomy, Physiology, Pathology, Physical and Chemical Properties, Technique for Collection, Examination, and Interpretation. The references are equally excellent—they begin with available sources concerned with Egyptian medicine and continue through 1959.

Neither the meticulous organization nor the rigid outline has resulted in a dead or a dry book; it is definitely alive and can be read with interest. As such, it can stand one criticism: The section dealing with the technic of obtaining pleural fluid omits the most important point—localization of the fluid fluoroscopically and aspirating with the patient in the exact position used for marking the effusion's peripheral location.

This book won First Prize in the first Modern Medical Monographs competition; it was well deserved.

B. W. A.

Clinical Disorders of Hydration and Acid-Base Equilibrium. 2nd Ed. By Louis G. Welt, M.D., Professor of Medicine, Department of Medicine, University of North Carolina. 336 pages; 22 × 15 cm. Little, Brown and Company, Boston, Massachusetts. 1959. Price, \$7.00.

This is an extremely well conceived exposition of current knowledge of body fluids as regards their volume, tonicity, composition, and acid-base balance. The author's thesis is deceptively simple: "Pathologic alterations in these functions represent dislocations from a normal equilibrium. . . ." This is in contrast to the easily accepted alternative which frequently leads us to believe that certain diseases produce specific, unique, pathophysiologic body water profiles.

With this thesis, normal physiology is considered in the first half of the book; the second half discusses clinical considerations. These are treated first as general problems; then in relation to specific clinical conditions. The discussion is brief and pointed and presented in an extremely readable fashion. The brevity is achieved without omission of important details, and very complete coverage of each topic is accomplished by numerical reference to a massive bibliography of 766 papers, books and monographs.

It is obviously easy to answer Dr. Welt's hope, expressed in the preface, that the material has been presented clearly and precisely. It is!

B. W. A.

Radiation Therapy. By WALTER T. MURPHY, M.D., Director of Therapeutic Radiology, Boswell Park Memorial Institute, Buffalo, New York. 1041 pages; 26 × 17.5 cm. W. B. Saunders Co., Philadelphia, Pa. 1959. Price, \$25.00.

This is a complete treatise on radiotherapy. All possible applications of radiotherapy in the treatment of malignant tumors are considered. In each group of tumors the important clinical and pathological features of the disease are considered along with the main ways of spreading with special reference to the lymph pathway and common lymph metastases.

The first chapter deals with the physical and biological factors affecting radiotherapy. The physical and radiobiological principles are mentioned in many other chapters as a basis for the detailed program of treatment.

The main features in each chapter are the indications for and technics of treat-

ment. Many technics are described, with practical information on set-up and dosimetry. In all chapters the possible combinations of different therapies are referred to with their main indications. Complications and results of therapy are given in the final portion of each chapter. The bibliography is complete and up to date.

This book is very useful to all persons interested in clinical radiotherapy of cancer. It represents a tremendous task performed by one of our leading radiotherapists; it reflects the result of a great deal of useful experience accumulated by treating a large number of patients for many years. The well-recorded experience and the keen clinical judgment of the author are obvious on each page of this publication.

This fundamental work is recommended to students and practitioners of radiotherapy.

F. G. B.

The Cerebrospinal Fluid: Production, Circulation and Absorption. Ciba Foundation Symposium. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Cecilia M. O'Connor, B.Sc. 335 pages; 21 × 14 cm. Little, Brown & Company, Boston. 1958. Price, \$9.00.

This volume on the production, circulation and absorption of the cerebrospinal fluid is a Ciba Foundation publication and includes the papers presented at a symposium on this subject held in May 1957. Most of the contributors are from the United Kingdom but others are from the United States and Europe. Different aspects of this problem are the subjects of 15 papers presented. Most of the papers are followed by a good bibliography and all are followed by a recorded discussion of the paper by the participants of the symposium.

This symposium considers the finer anatomy and physiology of the choroid plexus; experimental and clinical studies of the cerebrospinal pathways; the blood-spinal fluid and brain-spinal fluid barriers; some problems of spinal anesthesia, and the

effects of some vitamins on cerebrospinal fluid.

The volume is an excellent summary of current thinking and work on this perplexing problem. It will be of particular interest to anatomists, physiologists, and clinicians who deal with the nervous system. All students of the nervous system will read this volume with the greatest interest.

C. V. B.

Leukämie im Kindesalter: Beiträge zur Morphologie, Klinik, Pathophysiologie und Therapie (Abhandlungen aus dem Gebiete der praktischen Kinderheilkunde, Band 4). Von Dozent Dr. J. Oehme, Dr. W. Janssen und Dr. Ch. Hagitte; herausgegeben von Professor Dr. Albrecht Peiper. 169 pages; 24.5 × 17.5 cm. VEG Georg Thieme, Leipzig. 1958. Price, geb. DM 38.25.

Leukemia in Childhood is the fourth volume of a series of monographs devoted to

pediatric problems.

The presentation is systematic and clear, containing a full description of anatomic and hematologic features followed by differential diagnostic discussions and specific therapeutic recommendations. The monograph is obviously based on an extensive personal experience of the authors. Their own data are discussed in conjunction with those available from the international literature. Numerous graphs and tabular presentations of data are given. The illustrations are numerous, informative and of high quality. The bibliography is extensive; the omission of titles of papers is, however, regrettable. The book presents an excellent review of the present status

in the field which is clearly presented. Printing and reproduction of illustrations are of superb quality. The book is highly recommended.

A. G.

Reminiscences and Adventures in Circulation Research. By CARL J. WIGGERS, M.D., Professor Emeritus of Physiology, Western Reserve University, School of Medicine. 404 pages; 23.5 × 15.5 cm. Grune and Stratton, New York. 1958. Price, \$9.75.

This fascinating monograph is really two books in one: The first is devoted to the reminiscences of the author, and the second to his adventures in circulation research. Dr. Carl J. Wiggers, in the Foreword, outlines his endeavors, "... to recapture some of the incidents and accidents that have moulded my career, to recall some adventures in cardiovascular research and teaching, and to record some impressions of people, places, institutions, and organizations that have played a part in the advancement of the medical sciences during the past half century."

The book is well written, and provides a rare experience for the reader to participate in the academic and research experiences of the author. There are evaluations not of research technic alone, but of individuals. In book two, specific problems in circulation research are discussed with the perspective and evaluation of many years of broad research experience. Discussed in detail are the shortcomings of technics and of errors in interpretation.

This is a unique monograph, combining the autobiography of a cardiac researcher in the personal sphere with his laboratory experiences as well. It will occupy an important place among medical biographies and should prove of immense value not only to cardiac investigators but to medical students and physicians also.

LEONARD SCHERLIS

World Directory of Venereal-Disease Treatment Centres at Ports. 162 pages; 24 × 16 cm. (paper-bound). World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. 1959. Price, \$1.75.

The book contains an alphabetical list for every country and port of existing treatment centers for venereal diseases. For each center it provides the name and address, hours of operation, available hospital facilities, and whether or not treatment is administered free of charge.

The first such list was published in 1933. Since that time there have been four succeeding editions, including the present one. The first portion of the book is devoted to the Brussels Agreement of 1924 in which certain contracting countries made an effort to establish and maintain in each principal seaport available medical facilities for the treatment of venereal diseases. Such facilities were to be open to all merchant seamen without distinction of nationality.

It is interesting to note that this example of international cooperation by health authorities has been in existence for 26 years,

Although the book has been brought up to date regarding the treatment centers, it is interesting to note that in the personal booklet given to the patient, there is still mention of the drugs "Neoarsphenamine" and "Bismuth" even though these are no longer employed.

I believe this book would be greatly improved by the insertion of a paragraph on the more modern method of treatment.

H. M. R.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

- Acute Pericarditis. By DAVID H. SPODICK, M.D., Senior Physician and Chief, Cardiographic Laboratory of the Medical Services, Lemuel Shattuck Hospital, etc. 182 pages; 22.5 × 14 cm. 1959. Grune & Stratton, New York. Price, \$6.50.
- Antibiotic Therapy for Staphylococcal Diseases. Antibiotics Monographs No. 12. Edited by Henry Welch, Ph.D., Editor-in-Chief of Antibiotics & Chemotherapy and Antibiotic Medicine & Clinical Therapy, Washington, D. C.; and Maxwell Finland, M.D., Associate Professor of Medicine, Harvard Medical School, etc.; foreword by Félix Martí-Ibáñez, M.D. 208 pages; 23.5 × 15.5 cm. 1959. Medical Encyclopedia, Inc., New York. Price, \$4.50.
- Antithrombotic Therapy. Modern Medical Monographs 20. (Editor-in-Chief: IRVING S. WRIGHT, M.D.; Consulting Editor: RICHARD H. ORR, M.D.) By PAUL W. BOYLES, M.D., Instructor in Medicine, University of Miami School of Medicine, Jackson Memorial Hospital, Miami, Florida, etc. 131 pages; 22.5 × 14 cm. 1959. Grune & Stratton, New York. Price, \$5.00.
- Approaches to Research in Mental Retardation: Proceedings of the 1959 Woods Schools Conference Co-sponsored by the Technical Planning Project, American Association on Mental Deficiency, in Coöperation with Other Private and Governmental Agencies, May 1, 2, and 3, 1959, Philadelphia. (Reprinted from the American Journal of Mental Deficiency, Vol. 64, No. 2, September, 1959.) 205 pages; 25 × 17.5 cm. (paper-bound). 1959. American Association on Mental Deficiency, Post Office Box 96, Willimantic, Connecticut. Available at \$3 from AAMD Business Office, Post Office Box 96, Willimantic, Connecticut.
- Arterial Embolism in the Limbs: The Clinical Problem and Its Anatomical Basis. By A. L. Jacobs, M.A., D.M. (Oxon.), F.R.C.P., Physician to the Whittington Hospital, London; foreword by C. G. Rob, M.C., M.A., M.Chir. (Cantab.), F.R.C.S., Professor of Surgery, University of London, etc. 200 pages; 25.5 × 17.5 cm. 1959. The Williams & Wilkins Co., Baltimore, exclusive U. S. Agents. Price, \$8.00.
- Bulletins et Mémoires de l'École Nationale de Médecine et de Pharmacie de Dakar. Université de Dakar. Année 1958—Tome VI. 238 pages; 27 × 18 cm. (paperbound). 1959. Librairie Arnette, Paris.
- The Central Nervous System and Behavior: Transactions of the Second Conference, February 22, 23, 24 and 25, 1959, Princeton, N. J. Edited by Mary A. B. Brazier, Ph.D., Neurophysiological Laboratory, Massachusetts General Hospital, Boston, Mass. 358 pages; 24 × 16 cm. 1959. Sponsored by the Josiah Macy, Jr. Foundation, New York, N. Y., with the cooperation of The National Science Foundation, Washington, D. C. Price, \$4.75.
- A Guide to Antibiotic Therapy. By HENRY WELCH, Ph.D. 69 pages; 26 × 17.5 cm. 1959. Medical Encyclopedia, Inc., New York. Price, \$3.00.
- Human Biochemical Genetics. By H. HARRIS; with a foreword by L. S. Penrose, F.R.S. 310 pages; 22.5 × 14.5 cm. 1959. Cambridge University Press, Cam-

- bridge, England; available from Cambridge University Press, American Branch, New York, N. Y. Price, \$7.00.
- Immunological and Haematological Surveys: Report of a Study Group. World Health Organization Technical Report Series No. 181. 35 pages; 24 × 16 cm. (paper-bound). 1959. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.
- Le Laryngologiste et les Données Actuelles du Traitement des Insuffisances Respiratoires Aigues, Société Française d'Oto-rhino-laryngologie. Par Paul Aboulker, avec la collaboration de J. Lissac et O. Saint-Paul. 508 pages; 24 × 15.5 cm. (paper-bound). 1959. Librairie Arnette, Paris. Price, Broché 6.000 frs.
- Manual of Skin Diseases. By Gordon C. Sauer, M.D., Assistant Clinical Professor of Medicine (Dermatology) and Chief of the Section of Dermatology, University of Kansas School of Medicine, etc. 269 pages; 26 × 18 cm. 1959. J. B. Lippincott Company, Philadelphia. Price, \$9.75.
- The Physiological Basis of Diuretic Therapy. (Publication Number 366, American Lecture Series. A Monograph in the Bannerstone Division of American Lectures in Physiology, Edited by ROBERT F. PITTS, Ph.D., M.D.) By ROBERT F. PITTS, Ph.D., M.D., Professor of Physiology and Biophysics, Cornell University Medical College, New York, etc. 332 pages; 24 × 15.5 cm. 1959. Charles C Thomas, Publisher, Springfield, Illinois. Price, \$9.75.
- Las Proteinas y los Electrolitos Sanguineos en la Alergia Respiratoria. By Dr. Jorge Raul Vaccarezza. 61 pages; 27.5 × 18.5 cm. (paper-bound). 1959. Lopez & Etchegoyen, S. R. L., Buenos Aires. Price, m\$n 70.—
- Vom Symptom zur Diagnose: Lehrbuch der medizinischen Symptomatologie. Herausgegeben von Prof. Dr. W. Hadorn, Bern; Prof. Dr. W. Löffler, Zürich; Prof. Dr. R. Schoen, Göttingen; Prof. Dr. E. Uehlinger, Zürich; Prof. Dr. J. Waldenström, Malmö; Redaktion: Prof. Dr. W. Hadorn, Bern. 866 pages; 24.5 × 17.5 cm. 1960. S. Karger, Basel. Price, sFr. 79.—
- Treatment of Cancer in Clinical Practice. Edited by Peter B. Kunkler, M.A., M.D. (Cantab.), M.R.C.P., F.F.R., Radiotherapist, United Birmingham Hospitals, etc.; and Anthony J. H. Rains, M.S. (Lond.), F.R.C.S., Professor of Surgery, University of London, etc. 821 pages; 25 × 17.5 cm. 1959. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents. Price, \$19.00.
- Water Supply for Rural Areas and Small Communities. World Health Organization Monograph Series No. 42. By Edmund G. Wagner, Chief Engineer and Associate Chief of Field Party, Division of Health and Sanitation, Institute of Inter-American Affairs, Rio de Janeiro, Brazil; and J. N. Lanoix, Sanitary Engineer, Division of Environmental Sanitation, World Health Organization, Geneva, Switzerland. 337 pages; 24.5 × 16.5 cm. 1959. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, \$6.75.

New Journals

Cancer Current Literature Index. Will appear at intervals of two to three weeks, beginning with September, 1959. Each yearly volume will contain approximately

- 4,500 references from some 3,000 medical journals published all over the world, including those from the U.S.S.R. 32 pages; 24 × 16.5 cm. (paper-bound). 1959. Published by the Excerpta Medica Foundation, Amsterdam-New York, for the American Cancer Society, Inc., New York. Subscription price: \$7.50.
- Panminerva Medica: The Journal of the Italian Medical Association. A monthly review of Italian medicine. 62 pages; 29.5 × 20.5 cm. (paper-bound). 1959. Panminerva Medica, Corso Bramante 83–85, Torino, Italy. Subscription price: \$10.00.
- Psychopharmacologia. 88 pages; 23.5 × 15.5 cm. (paper-bound). 1959. Springer-Verlag, Berlin. Price: 1st issue, \$2.40; future issues to be published irregularly at varying prices, the total for a year to be approximately \$19.00.

MEDICAL NEWS

FUTURE MEETINGS

- April 6-9 The Annual Cardiovascular Seminar of the University of Mississippi School of Medicine at the Medical Center,
- May 16-18 The Annual Meeting of the National Tuberculosis Association at Los Angeles, California. Headquarters: Statler Hilton and Biltmore Hotels.

The American Trudeau Society will also meet at this time.

- May 23-28

 The Annual Convention of the American College of Cardiology at Indianapolis, Ind. Headquarters: Claypool Hotel. Exec. Dir., Philip Reichert, M.D., Empire State Building, New York 1, N. Y.
- June 13-17 The Annual Meeting of the American Medical Association at Miami Beach, Fla.
- Aug. 21–26

 The Third International Congress of Physical Medicine at Washington, D. C. Headquarters: Mayflower Hotel. Exec. Sec.,
 Dorothea C. Augustin, 30 North Michigan Avenue, Chicago 2, Ill.
- Sept. 13-15

 The Fourth National Cancer Conference of the American Cancer Society and the National Cancer Institute at Minneapolis, Minn. Coördinator: Roald N. Grant, M.D., American Cancer Society, Inc., Medical Affairs Department, 525 West 57th Street, New York 1, N. Y.
- Oct. 23–29 The Seventh Panamerican Congress of Gastroenterology in Santiago, Chile. Congress Office, Dr. Ricardo Katz, Hospital del Salvador, Casillar 70–D, Santiago, Chile.
- Nov. 29-Dec. 2 The American Medical Association Clinical Meeting at Washington, D. C.

EXAMINATIONS AND LICENSURE

June 17-18 American Board of Physical Medicine and Rehabilitation. Oral and written, at New York. Secretary, Earl C. Elkins, M.D., Mayo Clinic, Rochester, Minn.

Postgraduate Course

April 28-30 Congenital Heart Disease, the Second International Symposium on Changing Concepts in Medicine, at Philadelphia, Pa. Head-quarters: Deborah Hospital. Director, Charles P. Bailey, M.D., Deborah National Office, 901 Walnut Street, Philadelphia 7, Pa.

CARIBBEAN CRUISE

May 6-9

The Annual Texas Medical Cruise to the Caribbean, sponsored by the University of Texas Postgraduate School of Medicine. For physicians desiring AAGP credit, 25 hours of Category I teaching credit will be allowed.

SPECIAL TRAINEESHIP PROGRAM

The National Institute of Neurological Diseases and Blindness has announced a special traineeship program offering opportunity for advanced study and research training in neurological and sensory disorders, in the U. S. A. or overseas. Candidates must have an M.D., Ph.D., or equivalent degree; three years or more of post-doctoral training or experience in the field of training desired; and American citizenship or declaration of intent filed. The program is given for a period of not less than nine months, nor more than twelve. Awards may be renewed up to a total of 60 months. Stipends range from \$6,500 to \$17,500 per year and are determined individually. Application may be made to Chief of Extramural Programs, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda 14, Md.

FELLOWSHIPS

An Alan Gregg Travel Fellowship in Medical Education will be awarded to a member of the faculty of an American medical school by the China Medical Board of New York, Inc. The awardee will be enabled to undertake study in the areas of South Korea, Japan, Taiwan, Hong Kong, Philippines, South Vietnam, Thailand, Malaya, Indonesia or Burma, to increase his effectiveness as an educator. Study, travel expenses and a stipend will be provided. The candidate must be 30 to 55 years of age, an American citizen, hold a full-time faculty position in an American medical school and be recommended by the dean of that school. A written statement must be submitted stating what the candidate proposes to do if awarded a fellowship. Confirmation must be obtained from the host institution that the candidate is acceptable and that there are facilities available for his use. A personal interview is also required. Applications for fellowships should be made to the Director, China Medical Board of New York, Inc., 30 East 60th Street, New York 22, New York.

The National Foundation will award fellowships for clinical study in arthritis and related diseases to physicians who intend to apply their knowledge of these diseases to research, clinical service or teaching. The major portion of the candidate's program must be spent in clinical service with a minimum of research and teaching. The candidate must submit a program of full-time study in a hospital which, preferably, is university-affiliated. The fellowships will be awarded for a period of one year, but may be renewed. Further information from Division of Scholarships and Fellowships, Department of Professional Education, The National Foundation, 800 Second Avenue, New York 17, New York.

NEW CLINICAL CENTER STUDY

The Clinical Center, National Institutes of Health, has begun an investigation of the role of the adrenal gland in the Stein-Leventhal syndrome. The syndrome includes oligomenorrhea, hirsutism and polycystic ovaries. The laparotomy-proved cases of interested physicians are invited. The patients accepted will be studied for periods up to several weeks. The patients will then be returned to the care of their own physicians. The physician will receive a complete narrative summary. Follow-up visits to the Clinical Center may be arranged to supplement visits to the patient's own physician. Physicians interested in referring patients should write or telephone J. E. Rall, M.D., Chief, Clinical Endocrinology Branch, National Institute of Arthritis and Metabolic Diseases, Bethesda 14, Md. (Oliver 6–4000, Ext. 4181). Phone calls or referral letters will receive prompt attention. They should include all detailed information about the patient.

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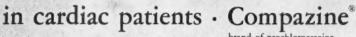
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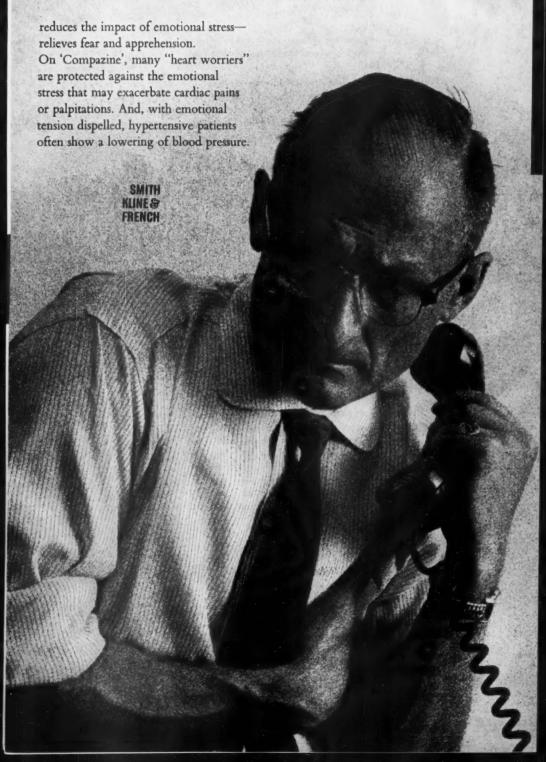


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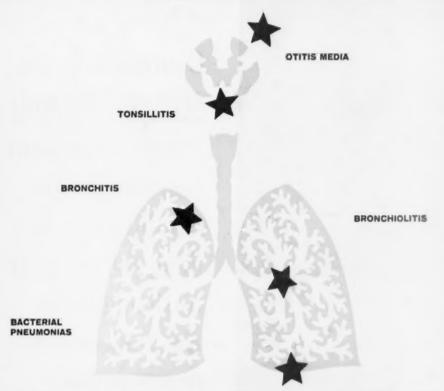
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1. Lysaught, J. N., and Cleaver, W.: Proceedings of the Detroit Symposium on Antibacterial
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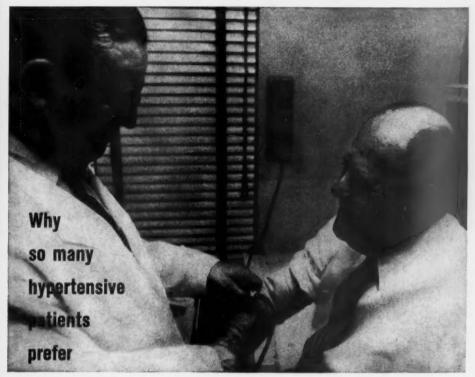
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*Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. 169:1609 (April 4) 1959.



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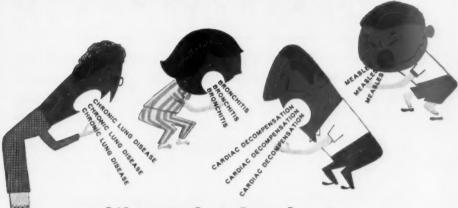
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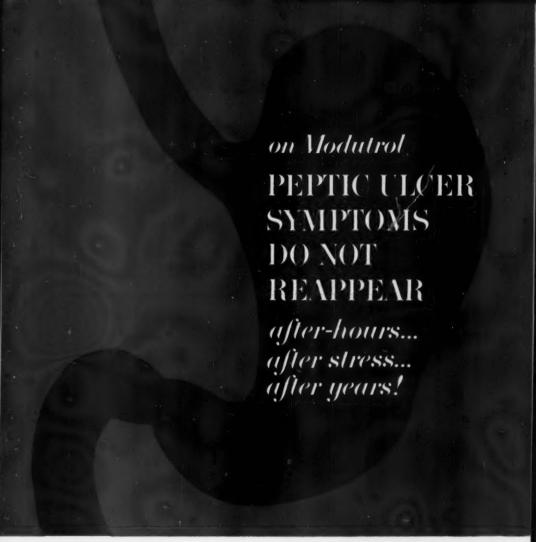
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1. Rosenblum, L. A.: Report, Symposium on Peptic Ulcer, Unive sity of Vermont School of Medicine, September 24, 1959.

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1. Kotkov, B.: Group psychotherapy with the obese. Paper read before The Academy of Psychosomatic Medicine, October 1958.



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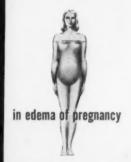


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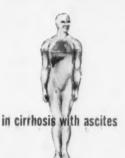
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"All three of the patients with Laennec's cirrhosis, ascites and edema had a favorable response, with a mean weight loss of 8 lbs., during the fiveday treatment period with a slight decrease in edema." Castle, C. N., Conrad, J. K. and Hecht, H. H.: Arch. Int. Med., 103:415, (March) 1959.



"In a study of 10 patients with the nephrotic syndrome associated with various types of renal disease, orally administered chlorothiazide was a successful, and sometimes dramatic, diuretic agent." Burch, G. E. and White, M. A., Jr.: Arch. Int. Med., 103:369, (March) 1959.



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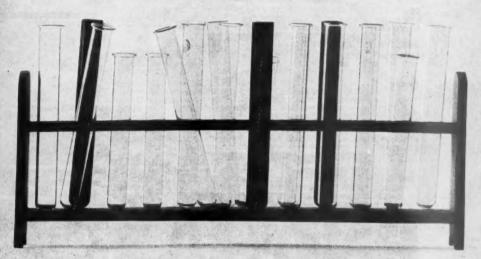
"RISTOCETIN IS AN EFFECTIVE PRIMARY AGENT IN STAPHYLOCOCCAL INFECTIONS!"

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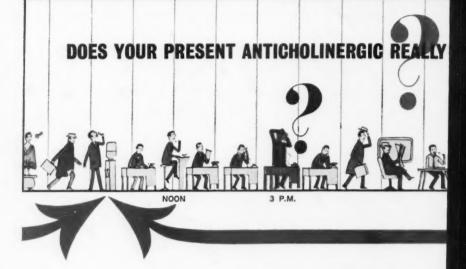
(Ristocetin, Abbott)

conclusions—"Ristocetin is an effective primary agent in staphylococcal infections, as well as in short-term therapy of enterococcal endocarditis. It is administered intravenously; intermittent, rapid infusion is recommended. Ristocetin is bactericidal in concentrations attained by this technique... The hematological and other side effects such as phlebitis, skin eruptions, and fever are infrequent with the recommended dosage schedules and mode of administration. The dosage of ristocetin is reduced in renal insufficiency since the antibiotic tends to accumulate.

INDICATIONS: Against staph-, strep-, pneumo- and enterococcal infections. A drug of choice for serious infections caused by organisms that resist other antibiotics. DOSAGE: Administered intravenously. A dosage of 25 mg./Kg. daily will usually be adequate for strep-, pneumo- and enterococcal infections. Most staphylococcal infections will be controlled by 25 to 50 mg./Kg. daily. SUPPLIED: In vials containing a sterile, lyophilized powder, representing 500 mg. of ristocetin A activity.



1. Romansky, M. J., Ristocctin, Antibiotics Monographs, No. 12, New York, Medical Encyclopedia Inc., 1959.



The test—you might say the acid test—of an anticholinergic is simple: will it protect your patient from hyperacidity around the clock, even while he sleeps. The weakness of t.i.d. or q.i.d. preparations is well recognized; but even some "b.i.d." encapsulations may be unreliable. McHardy, for instance, found a "widely variable duration of action, definitely less than that anticipated" in the "sustained," "delayed," and "gradual release" anticholinergics he studied.

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OBSERVE THE OXYPHENCYCLIMINE REPORTS...

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Does the medication you now prescribe assure you of all these benefits? If not, why not put your next patient with peptic ulcer or G.I. dysfunction on therapy that does.

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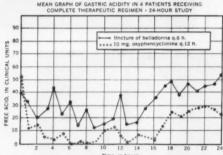
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Jackson, D., and Oakley, W.: Lancet 2:752, 1959.

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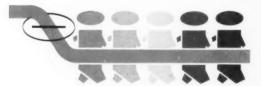
"This drug was more potent, and smaller dosages could be used. This increases the ease of administration as well as reduces the economic factors involved."

Knox, L. J., and Doenges, J. P.: Am. J. M. Sc. 238:427, 1959.

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Reference E. Dunemore, R.A., et Am. J. H. Se, 236:483 (Oct.) 1956
Blancier, P., & al.: Univ. Michago. M. Bulf. 20:409 (Oct.) 1958. 3. Smirk
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□ good to excellent response in a vast majority of patients—"Low doses...provided rapid and effective relief...in almost all of the 157 patients treated..."1"...appeared to be superior as an intra-articular injectable substance to anything hitherto available."2

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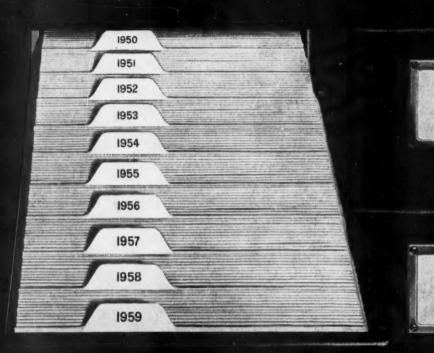
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1. Bartels, E. C., and Matossian, G. S.: Gout: Six-Year Follow-Up on Probenecid (BENEMID) Therapy, Arthritis and Rheumatism 2:193, June 1959.

BENEMID is "remarkably free from toxic side reaction....Patients tolerate the drug well. "2

2. Lockie, L. M., and Talbott, J.: Does Your Patient Have Gout?, Scientific Exhibit, American Medical Association, New York City, June 3-7, 1957.

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 Kron, K. M., Hermann, I. F., Smith, R. T., and Richards, J. C.: Which Rheumatic Disease?, Scientific Exhibit, American Medical Association, Atlantic City, June 8-12, 1959.

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More than an antacid is needed. Kolantyl is more than an antacid. It blocks all three sources of ulcer pain. An antispasmodic (safe Bentyl) to stop pain-producing spasm, Anti-enzyme action to curb peptic erosion. Balanced laxate. Plus a demulcent to promote healing. TRADEMARKS: BENTYLS, KOLANTYLS

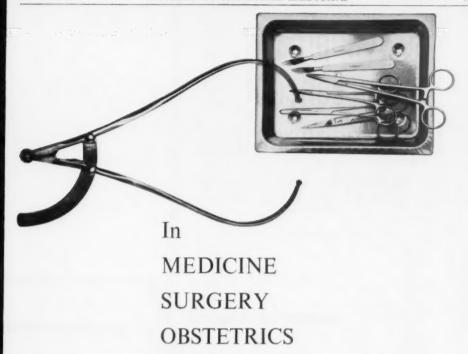
Shotgun therapy? Probably not, when you consider this: Which one of the ingredients of Kolantyl can an ulcer patient do without?

Dosage: 1 teaspoonful, or 2 tablets every three hours, as needed.

REFERENCES: 1. Altschule, Mark D.: Med. Science 6:560, Oct. 25, 1959. 2. Kasich, A. M.; Baleman, A. P., Jr., and Rafsky, J. C.: Am. J. Digest. Dis. 1:361, 1956. 3. Roth, J. L. A.; Wechsler, R. L., and Bockus, antacids that neither constipate nor . H. L., Gastroenterology 31:493, 1956. 4. Rafsky, J. C.: Gastroenterology 27:29, 1954. 5. Ruffin, J. M.; Baylin, G. J.; Legerton, C. W., and Texter, E. C., Jr.: Gastroenterology 23:252, 1953.

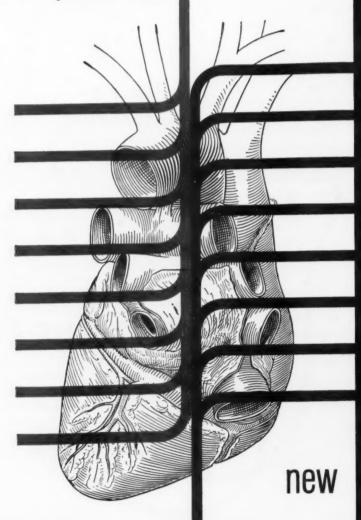
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| Patients | Age | Diagnosis | Usual Dose | Duration of Treatment |
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| 31 | 40's-70's | Angina pectoris. "About one-half were severely ill." | 15-30 mg/day | 1-9 mos. |

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References: 1. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 2. G. C. Griffith, Clin. Med., 6:1555, 1959.



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Complete Control of
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| Grand Mal Psychomotor Focal Jacksonian | 214 29 19 | 172 (80%) 19 (65%) 19 (100%) | 15 (7%) | 27 (13%) 10 (35%) | | |

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| Type of Seizure | Number of Patients | Completely Controlled | 50-90% Improved | <50% |
|--------------------|-----------------------|-----------------------|--------------------|-------------|
| Grand Mal | 613 | 175 (28.5%) | 253 (41.2%) | 185 (30.3%) |
| Psychomotor | 130 | 10 (7.7%) | 65 (50%) | 55 (42.3%) |
| Focal Jacksonian | 92 | 14 (15.2%) | 36 (39.1%) | 42 (45.7%) |

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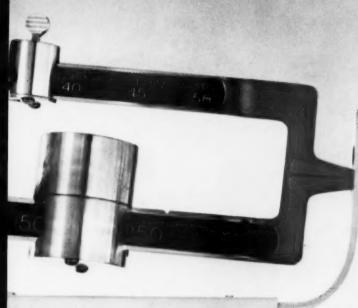
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Cornely, D. A., and Ritter, J. A.: N-acetyl-p-aminophenol (Tylenol Elixir) as a Pediatric Anti-pyretic-Analgesic, J.A.M.A. 160:1219 (Apr. 7) 1956.
 Mintz, A. A.: Management of the Febrile Child, J. Ky. Acad. Gen. Pract. 5:26 (Jan.) 1959.







fluid weight loss: A MEASURABLE RESPONSE TO ESICTIX

(See response of patients with edema on following pages)→



in congestive heart failure

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5 pounds lost in 4 days; 4+ pitting cleared; hepatic congestion and râles cleared; patient ambulatory







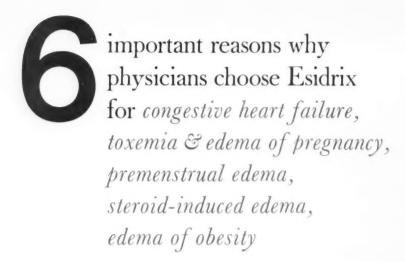
27 pounds lost in 19 days; abdominal swelling and pedal edema cleared

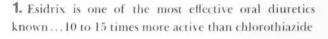






10 pounds lost; pitting edema cleared in 5 days; copious urine output, yet serum electrolytes remained within normal range





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1. Babcock, G., Jr., and Packard, L. A.: Clin. Med. 6:985 (June) 1959.

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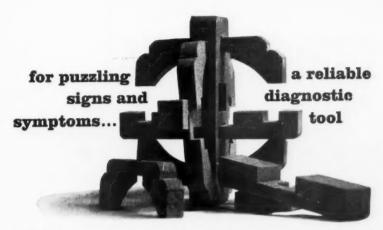
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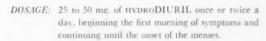
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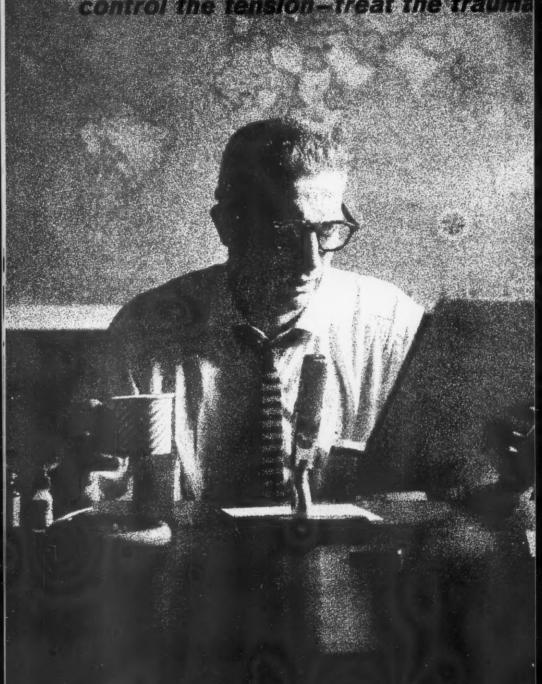
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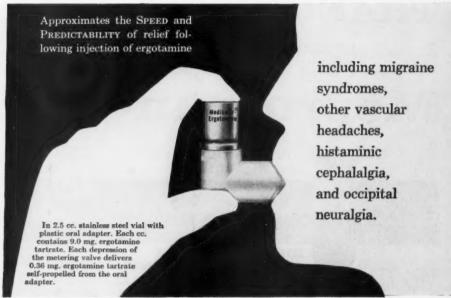
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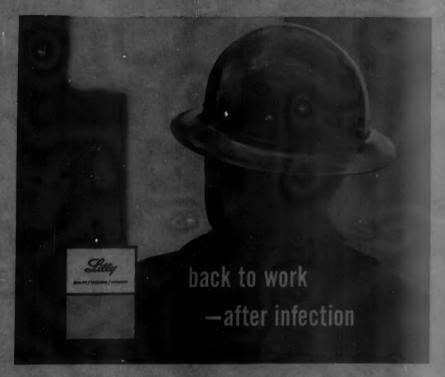
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